Rhodium catalysed intermolecular chelation controlled hydroacylation

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Award date:
2006

Awarding institution:
University of Bath

UNIVERSITY OF BATH

Rhodium Catalysed Intermolecular Chelation Controlled Hydroacylation

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A thesis submitted for the degree of Doctor of Philosophy

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October 2006

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Abstract

Hydroacylation is a relatively new and little explored process which is highly atom economic and potentially an attractive process. Intramolecular systems have become valuable tools for the formation of 5-membered rings with enantioselective versions now known. The range of substrates for other ring sizes and in particular intermolecular systems is still very limited and often high temperatures and pressures are needed for effective reactions.

Recently a large amount of work has been carried out to extend the range of substrates and improve the conditions needed for reaction. Many methods of reducing the problem of competitive decarbonylation have been explored and new systems using both additives and chelation strategies have led to the formation of acyclic ketone products. The range of substrates able to react with aldehydes has been extended to include alkynes leading to useful enone products. Despite these advances there is still no general method for the hydroacylation of aliphatic aldehydes.

In this thesis some background into hydroacylation and the recent developments will be outlined. It will then discuss the development of a range of aldehydes with β-sulfur atoms, acting as chelating substrates, which can efficiently react with a range of alkenes, alkynes and allenes. An improvement to the catalyst system will be reported along with some evidence as to why this new system is beneficial. Lastly the first enantioselective intermolecular hydroacylation reaction will be explored using allenes as substrates.

Acknowledgements

Firstly a big thank you to Mike Willis for his unending enthusiasm for the project and all his ideas and help. To Gordon Currie an equal thank you for making me so welcome on placement and putting up with all the smelly chemicals I brought with me. Also thank you to 'Team Rhodium' especially Rob Woodward and James Osborne who were always ready with ideas when mine were running out. I am also grateful to Andy Weller and Gemma Moxham for their work on the inorganic side of the catalyst project. Also thank you to the EPSRC Mass Spectrometry service for all their work, and the technical staff at the University of Bath.

A huge thank you to all the members of the Willis group past and present for making it a fun three years especially those in Lab 0.26 for putting up with my endless singing, Luke, Dawn, Gareth, Gary, Jay, Simon, Matt, Ana, Rob, Fletch, Ai, Jimmy, Nikki, Andy, Roy, Scott and Bax. Also, to all those who did proofreading, thank you very much, Fletch, Matt, Scott, Nikki and Jimmy especially. A special thank you goes to Simon who survived the three years with me and taught me all I know about the world of sport.

Thanks and lots of love to my Mum, Dad, Paula and Andrea for all their encouragement over the many years of education. Last, but not least, thanks and all my love to Ben for reminding me there is life outside of chemistry, and supporting me in every possible way, particularly over the last few months, I couldn't have done it without you.

Contents

List of abbreviations

In order to conserve space, the following list of abbreviations will be used throughout:

Å	-	angstrom
Ac	-	acetyl
acac	-	acetylacetonate
app.	-	apparent
aq.	-	aqueous
Ar	-	aryl
Atm.	-	atmosphere
(*R,R*)-BDPP	-	(2*R*, 4*R*)-2,4-*bis*(diphenylphosphino)pentane
BINAP	-	2,2'-*bis*(diphenylphosphino)-1,1'binaphthyl
Bn	-	benzyl
br.	-	broad
Bu	-	*n*-butyl
n-BuLi	-	*n*-butyl lithium solution
(*R,R*)-Me-BPE-		1,2-*bis*((2*R*, 5*R*)-2,5-dimethylphospholano)ethane
*i*Bu	-	*iso*-butyl
t-Bu	-	tertiary butyl
°C	-	degrees centigrade
(*S,S*)-Chiraphos	-	(2*S*,3*S*)-*bis*(diphenylphosphino)butane
CI	-	chemical ionisation
COD	-	1,5-cyclooctadiene
COE	-	cyclooctene
COT	-	cyclooctatetraenide
Cp*	-	1,2,3,4,5-pentamethylcyclopentadienyl
Cy	-	cyclohexyl
d	-	doublet
DCE	-	dichloroethane
DCM	-	dichloromethane
DIBAL-H	-	di*iso*butyl aluminium hydride

DIOP	-	2,3-*ortho*-isopropylidene-2,3-dihydroxy-1,4-*bis*(diphenylphosphino)propane
DIMPC	-	1,2-*bis*(diphenylphosphinomethyl)cyclohexane
(*R,R*)-DIPAMP-		(1*S*, 2*S*)-*bis*[(2-methoxyphenyl)phenylphosphino]ethane
DME	-	1,2-dimethoxyethane
DMF	-	*N,N*-dimethylformamide
DPEphos	-	*Bis*(2-diphenylphosphino)-phenyl ether
dppb	-	1,1-*bis*(diphenylphosphino)butane
dppe	-	1,2-*bis*(diphenylphosphino)ethane
dppf	-	1,1-*bis*(diphenylphosphino)ferrocene
dppp	-	1,3-*bis*(diphenylphosphino)propane
e.e.	-	enantiomeric excess
EI	-	electron impact
Eq.	-	equivalent
ES	-	electrospray
Et	-	ethyl
(*R*)-Et-Duphos-		1,2-*bis*(2,5-diethylphospholano)benzene
g	-	gram
h	-	hour
hex	-	hexyl
HPLC	-	high performance liquid chromatography
HRMS	-	high resolution mass spectrum
Hz	-	hertz
IR	-	infrared
J	-	coupling constant
Josiphos	-	[2-(diphenylphosphino)ferrocenyl]ethyl dicyclohexylphosphine
L	-	ligand
LDA	-	lithium diisopropylamide
lit.	-	literature
M	-	molar
m	-	multiplet
m-	-	*meta*
Me	-	methyl
MeCN	-	acetonitrile

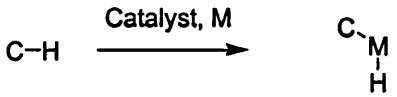
(*R*)-Me-Duphos	-	1,2-*bis*(2,5-dimethylphospholano)benzene
MOP	-	2-diphenylphosphino-2'-methoxy-1,1' binaphthyl
MHz	-	megahertz
min	-	minutes
mmol	-	millimole
m/z	-	mass to charge ratio
NBD	-	bicyclo[2.2.1]hepta-2,5-diene
NBS	-	*N*-bromosuccinimide
NMR	-	nuclear magnetic resonance
Nu	-	nucleophile
o-	-	*ortho*
oct	-	*n*-octyl
p-	-	*para*
pent	-	pentyl
Ph	-	phenyl
PPh_3	-	triphenylphosphine
ppm	-	parts per million
Pr	-	propyl
*i*Pr	-	isopropyl
*i*Pr-Duphos	-	1,2-*bis*(2,5-diisopropylphospholano)benzene
(*R*)-Prophos	-	*R*-1,2-*bis*(diphenylphosphino)propane
Py	-	pyridine
(*R*)-QUINAP	-	(*R*)-1-(2-diphenylphosphino-1- naphthyl)isoquinoline
q	-	quartet
R	-	generic group/substituent
Red-Al	-	sodium *bis*(2-methoxyethoxy)aluminium hydride solution
r.t.	-	room temperature
s	-	singlet
sol.	-	solution
(*R*)-SpiroP	-	1*R*, 5*R*, 6*R*-1,6-*bis*(diphenylphosphinoxy)spiro[4.4]nonane
t	-	triplet
(*S,S,R,R*)-Tangphos	-	(1*S*, 1*S*, 2*R*, 2*R*)-1,1'-di-*t*-butyl[2,2]-diphospholane
Tf	-	trifluoromethanesulfonate
THF	-	tetrahydrofuran

THP	-	tetrahydropyran
TLC	-	thin layer chromatography
(*R*)-Tol-BINAP	-	(*R*)-2,2'*bis*-(di-*p*-tolyl-phosphino)-1,1'-binaphthyl
(*R*)-TUNEPHOS	-	*R*-1,13-*bis*(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin
Xantphos	-	9,9-dimethyl-4,6-*bis*(diphenylphosphino)xanthane

1 Introduction

1.1 C-H bond activation

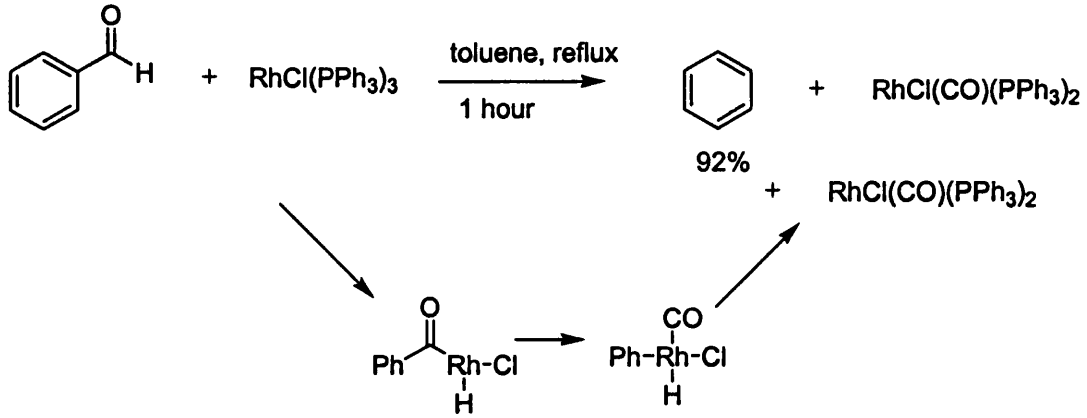
Metal catalysed C-H bond activation is now widely used in many forms, from oxidation reactions to coupling, isomerisations and in particular C-C bond forming reactions, with several reviews now available.[1-4] C-H bonds were traditionally thought to be unreactive but this view was revolutionised by the discovery that certain transition metals including Pt, Pd, Rh, and Ru, are able to activate these bonds thus making reactions possible. This activation is accomplished by converting the strong C-H bond to a weaker C-metal-sigma bond by a process of oxidative addition (scheme 1).[5, 6]



Scheme 1 : Metal catalysed C-H bond activation

1.2 C-H activation of aldehydes

Over the last century the range of reactions employing C-H activation has expanded greatly, including reactions such as decarbonylation and hydroacylation. These reactions utilise the C-H bond of an aldehyde unlike the majority of reactions performed with aldehydes which involve the carbonyl group. Both reactions are closely linked but while decarbonylation has been proven to be a very useful synthetic process (scheme 2), hydroacylation is still in its infancy.

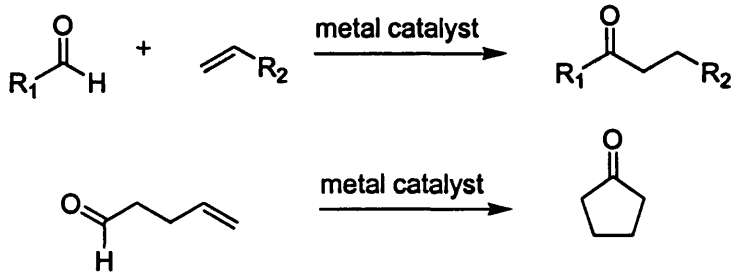


Scheme 2: Example of decarbonylation[7]

Despite commercial success, decarbonylation started out as a process stoichiometric in rhodium because one of the products of the reaction is the inactive catalyst, *trans*-$RhCl(CO)(PPh_3)_2$. In general decarbonylation reactions require very high temperatures and pressures because dissociation of the carbon monoxide from the metal to regenerate the catalyst is very slow at temperatures below 200°C.[7] Improvements have been made by adding a CO abstraction reagent e.g. $P(O)(OPh)_2N_3$, which allows the reaction to become catalytic at room temperature as shown by O'Connor *et al.*[8] This improvement is, however, limited to primary aldehydes. The reaction has been successfully carried out using Ru(II) as well as Rh(I).[9, 10]

1.3 Hydroacylation

The first hydroacylation reaction was discovered during an investigation into the synthesis of natural products.[11] Hydroacylation is defined as the addition of an acyl group and hydrogen atom across an unsaturated C-C bond. A basic example is the addition of an aldehyde across an alkene to form a ketone. Both intra- and intermolecular variations of the reaction are known (scheme 3).



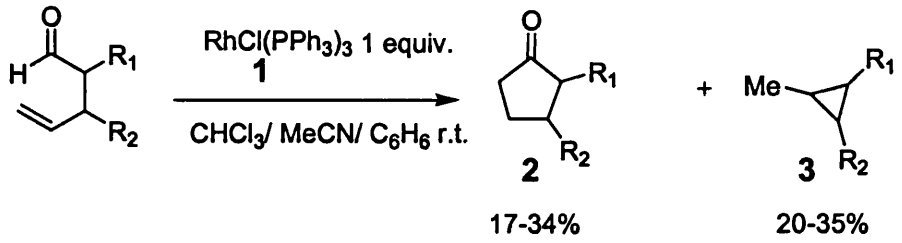
Scheme 3: Intermolecular and intramolecular hydroacylation

As hydroacylation is atom-economical, and does not create any by-products, it is a very attractive reaction.[12] Therefore if a generalised procedure with a large variety of unsaturated compounds could be reacted with a large number of aldehydes this would represent an economical and environmentally favourable process. At the present time, however, limited substrates are known to work within the reaction. Significant

advances have been made in recent years leading to more successful and generalised systems, as will be outlined below.

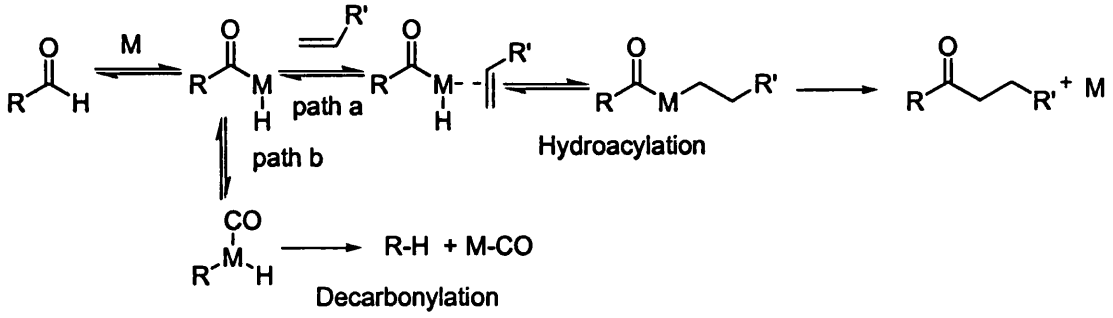
1.4 Intramolecular hydroacylation

In 1972 Sakai and co-workers first reported an intramolecular hydroacylation using Wilkinson's complex (1) in stoichiometric quantities while they were researching the synthesis of prostaglandins.[11] As can be seen in scheme 4 along with the hydroacylation product (ketone 2), cyclopropane products (3) were isolated in similar yields.



Scheme 4: First reported hydroacylation reaction[11]

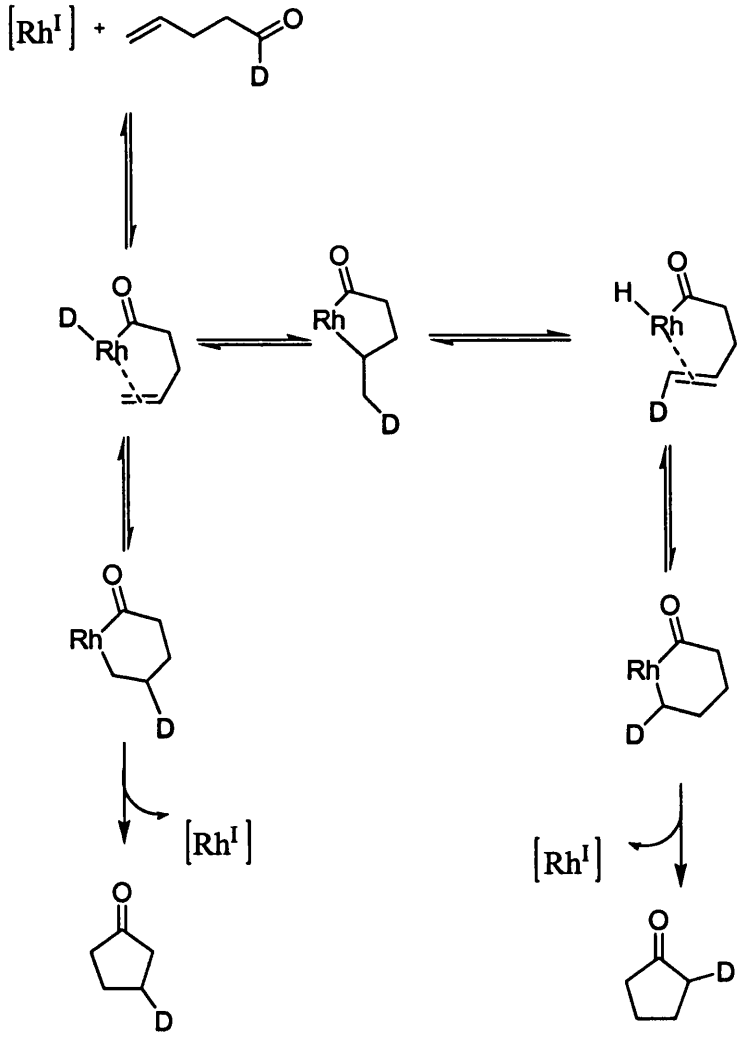
The majority of problems in hydroacylation arise from competitive decarbonylation due to the similar mechanisms involved in both processes (scheme 5). In both processes oxidative addition of the metal into the aldehyde C-H bond is the initial step. With decarbonylation, the oxidative addition is followed by migration of the carbonyl group, which produces an inactive catalyst after reductive elimination. This explains why stoichiometric amounts of rhodium were needed in the early examples.



Scheme 5: Competitive processes of hydroacylation and decarbonylation[5]

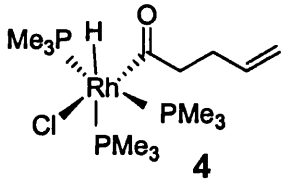
In intramolecular reactions the olefin is in close proximity to the metal centre after oxidative addition and so the addition of the acyl group across the unsaturated bond is relatively easy. This process is therefore competitive with decarbonylation.

Many improvements have been made since the first report as various groups began to investigate the scope of the reaction and the mechanistic aspects behind it. One of the first groups to investigate the mechanism was Miller *et al.* using Wilkinson's complex.[13] They determined the first step in the mechanism is the oxidative addition of the aldehyde C-H bond to the rhodium. This is followed by coordination of the alkene, hydride addition to the alkene functionality and finished by reductive elimination. Deuterium labelling studies performed by Miller showed that the majority of the deuterium was in the expected beta-position but around 10% occurred in the α position.[14, 15] This result led Miller to propose the mechanism shown below (scheme 6) indicating a reversible β-hydride delivery.



Scheme 6: Mechanism for hydroacylation proposed by Miller

This study was supported by the work of Milstein who was able to isolate and characterise the acylrhodium (III) hydride intermediate **4** by employing a different phosphine ligand.[16] Using $RhCl(PMe_3)_3$ at room temperature gave complex **4** shown in figure 1 with the acyl unit trans to the chloride ligand.



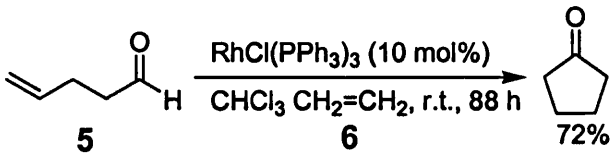
4

Figure 1: Isolated *cis*-hydridopent-4-enoylrhodium (III) complex[16]

This complex is stable enough to undergo characterisation due to the slow dissociation of the trimethylphosphine ligands. When this complex was heated to 50 °C the reaction proceeded to completion to give an intramolecular hydroacylation product as well as a small amount of the decarbonylated material. This shows that this intermediate is a valid step in the mechanistic scheme.

1.41 Sub-stoichiometric systems

Miller and co-workers were also the first to achieve sub-stoichiometric levels of catalyst by using an ethylene saturated solvent.[17] This gave them cyclopentanone **7** from acyclic 4-pentenal **5** in good yield using a 10% loading of Wilkinson's complex **1** in ethylene **6** saturated chloroform.

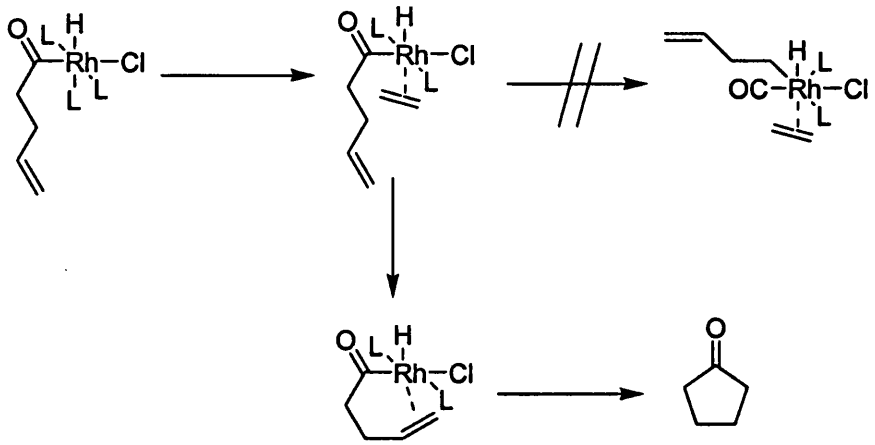


5 **6** **7**

Scheme 7: Intramolecular hydroacylation with ethylene saturation

Even in this early reaction there were signs of intermolecular hydroacylation, as some of the products from the intermolecular reaction of ethylene and pentanal were isolated, however the yields of these products were extremely low. It was believed that the ethylene inhibits decarbonylation by forming a co-ordinately saturated

rhodium species. As the rhodium does not have a free site, the carbonyl group cannot migrate and form the inactive rhodium-carbonyl species. This allows the lower catalyst loadings to be successful. The addition of other olefins or acetylenes were not as effective at suppressing the decarbonylation. During these studies it was reported that water did not have an effect on the yield of the reaction although oxygen destroyed the catalyst.



Scheme 8: Ethylene reducing decarbonylation

This same methodology was employed by Larock, however instead of using Wilkinson's complex (**1**) he used a catalyst system generated *in situ* from $[Rh(COD)Cl]_2$ (**8**) and $P(4\text{-}MeC_6H_5)_3$, $P(4\text{-}MeOC_6H_5)_3$ or $P(4\text{-}Me_2NC_6H_5)_3$.[18] This system allowed substrates including spirocycles **9** and fused cyclopentene **10** and **11** products to be synthesised. However, high catalyst loadings (50%) were needed and only five-membered rings could be created as no other ring sizes were successfully synthesised by this method.

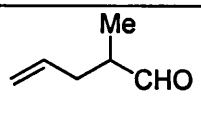
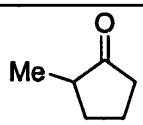
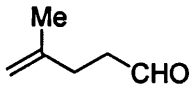
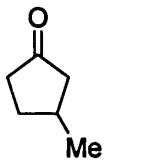
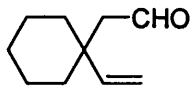
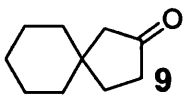
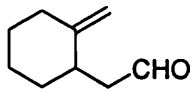
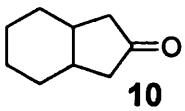
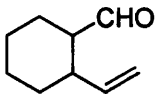
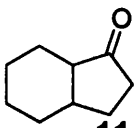
entry	aldehyde	product	yield (%)
1			51
2			90
3		 **9**	93
4		 **10**	90
5		 **11**	89

Table 1: Intramolecular hydroacylation with ethylene saturated solvent

Bosnich *et al.* extended work on the mechanism and scope of the reaction by using the rhodium (I) species $[Rh(diphos)]_2(ClO_4)_2$.[19, 20] This move to cationic complexes allowed a much larger range of reactivity to be explored as well as allowing lower catalyst loadings without the need for ethylene saturation. Using a range of phosphine ligands they showed that diphosphines generally gave high turnovers and are catalytically active, while monodentate phosphines generally gave poor turnovers because of competitive decarbonylation. They also established that the catalytically active species was the monomeric $[Rh(diphos)]^+$ species rather than the dimer. The most active system was found to be $[Rh(dppe)]ClO_4$ **12** which can be prepared *in-situ* from hydrogenation of $[Rh(dppe)(NBD)]ClO_4$ or isolated as the arene-bridged dimer.

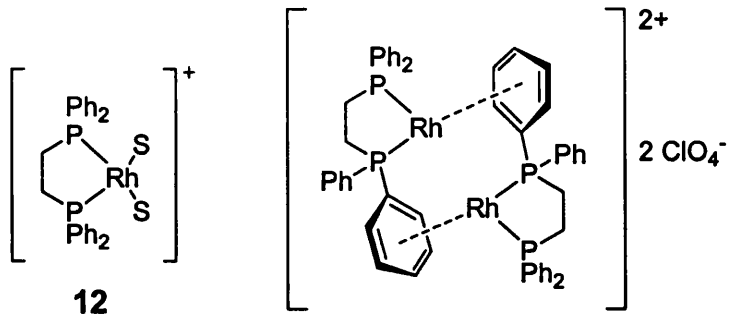


Figure 2: Active states of $[Rh(dppe)]^+$

The $[Rh(dppe)]ClO_4$ catalytic system was used to study the cyclisation of 4-pentenals. The cationic catalysts were reported to have several advantages. The authors proposed that the cationic rhodium complex would undergo rapid oxidative addition because of the coordinative unsaturation of the rhodium atom and with 4-pentenals the additional stabilisation through the coordination of the olefin. Due to the favourable alignment of the metal-hydride bond in the hydrido-acyl intermediate, hydride transfer was also predicted to be fast. Lastly, the reductive elimination was also thought to be fast due to the coordinative unsaturation of the catalyst based on previous observations with other systems. It was also argued decarbonylation would be less favourable than in complimentary processes using Wilkinson's complex **1** due to the positive charge on the $[Rh(dppe)]^+$ system.

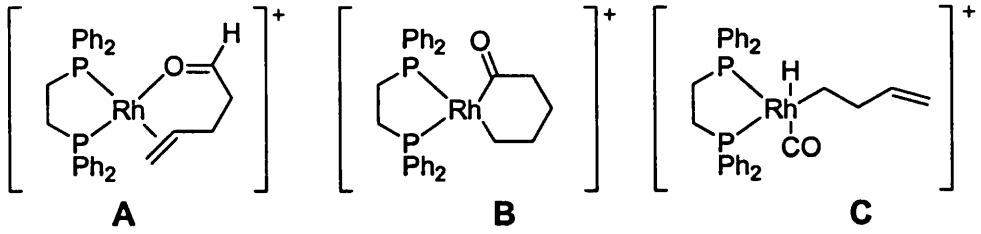


Figure 3: Reactive states of $[Rh(dppe)]^+$ in the hydroacylation reaction

This catalyst was able to work at low catalyst loadings (1 mol%) in a number of reactions that allowed the system to be more synthetically useful. The catalyst was effective at room temperature for a range of aldehydes with various substitutions however only five-membered ring formation was possible (Table 2).

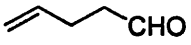
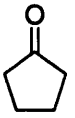
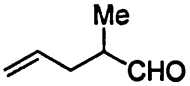
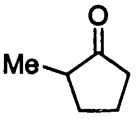
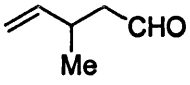
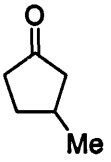
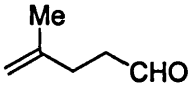
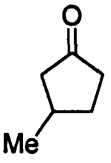
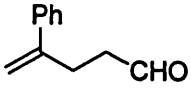
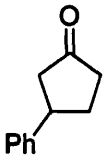
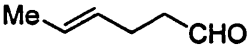
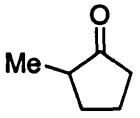
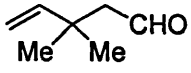
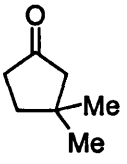
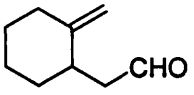
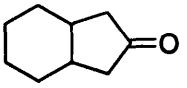
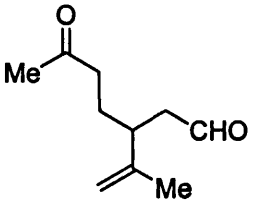
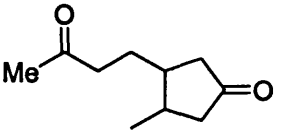
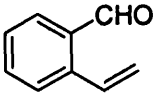
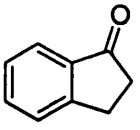
Entry	Aldehyde	Catalyst mol%	product	Yield (%)
1		1		95
2		1		88
3		1		98
4		1		98
5		2		92
6		4		89
8		1		100
9		1		90 35:65 *cis:trans*
10		2		94 42:58 *cis:trans*
11		2		89

Table 2: Intramolecular hydroacylation with [Rh(dppe)]ClO_4[19]

Bosnich conducted mechanistic studies using their new catalyst system. Both kinetic experiments and deuterium labelling studies were performed, unfortunately without isolating or observing any intermediates. The group reported this was probably due to the fact that at any stage the majority of the material was outside the catalytic cycle. They also conducted extensive NMR experiments and several observations were made. These concluded that there was substrate inhibition of the catalyst and in a similar vein a reduction in decarbonylation was also observed with higher substrate : catalyst loadings. This is accounted for by the same reasoning as the observation of ethylene stabilisation mentioned earlier, where a second molecule of substrate can lead to a saturated rhodium species through coordination to the alkene portion (figure 4).

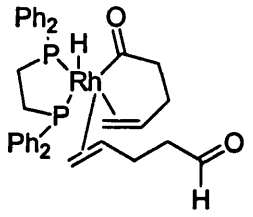
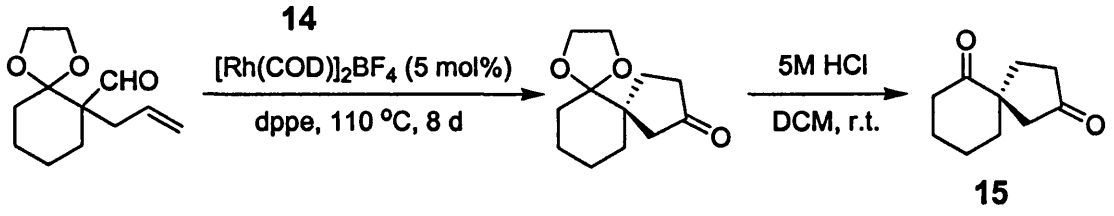


Figure 4: Extra stability provided by coordination to second molecule of aldehyde

Due to this second molecule coordinating, a balancing act must be made with the concentration of catalyst, between turnover number and turnover rate. Deuterium studies showed extreme scrambling of deuterium onto virtually all the carbons of unreacted pentenal and at positions two and three of the cyclopentanone product. It was concluded that the C-H activation is a rapid but reversible process and that other deuterium scrambling occurs due to a more complex mechanism than previously thought. They proposed that all stages except the final reductive elimination were fast and reversible with the reverse steps being much faster than the forward ones. It was therefore suggested that the substrate goes through many attempts at surmounting the final rate limiting turnover step. They additionally reported that carbonyl de-insertion and reinsertion are very rapid processes but irreversible carbonylation of the catalyst is an infrequent event. They were not able to isolate any of the intermediates to support these theories. [20]

This catalyst system has been adopted by several groups working on both intramolecular[19, 21, 22] and intermolecular[23-25] reactions including the Fu group and the Willis group among others.

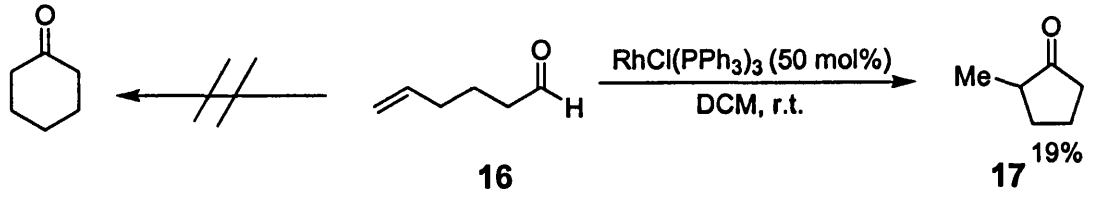
It has also been possible to apply hydroacylation to more synthetically complex structures. The Undheim group have used hydroacylation methodology to synthesise spiranediones using $[Rh(COD)_2]BF_4$ **14**.[21] Although the reaction time for this reaction was extremely long the relatively low catalyst loadings allow the access to synthetically interesting spiranediones **15**. This reaction was carried out in the absence of any solvent to minimise decarbonylation.



Scheme 9: Synthesis of spiranediones

1.42 Larger Ring Synthesis

Ring systems larger than five are significantly more difficult to form using hydroacylation for several reasons. One problem encountered is the formation of medium ring sized metallocycle intermediates. These lead to smaller than expected ring sizes as 5-membered rings, if possible, are always the preferred product. For example 5-hexenal **16** is capable of hydroacylation but yields 2-methyl-cyclopentanone **17**.[18]

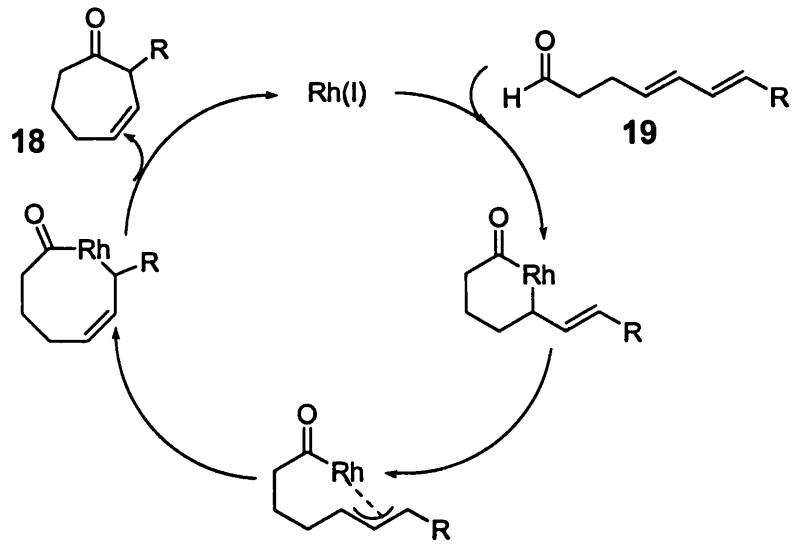


Scheme 10: Cyclisation of 5-hexenal

Ring closure with larger ring sizes is often slower and therefore decarbonylation can also become an issue.

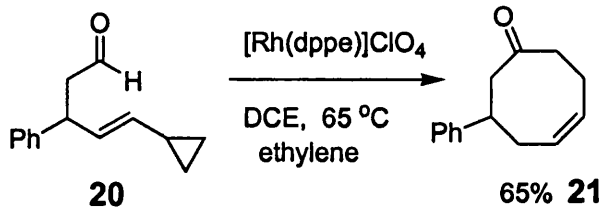
Several methods forcing the formation of larger ring sizes have been investigated. For example using a rigid carbohydrate derived backbone gave exclusively the cyclohexanone product.[26] The authors reasoned this was due to the ring strain that would be present in the 5,5,5-tricyclic product. This theory was supported by the slow formation of the cyclopentanone from a vinyl analogue. However this strategy is limited to few substrates and therefore not suitable as a general synthetic method.

Another approach to the synthesis of medium sized rings is to incorporate appropriate functionality into the substrates. The Mori group have applied this strategy to give cycloheptanone **18** products from the cyclisation of 4,6-dienals **19** (scheme 11).[27] After the initial oxidative addition and olefin insertion the second alkene bond is capable of conjugation with the intermediate and ring expansion can occur through a π-allyl rhodium intermediate.



Scheme 11: Formation of cycloheptanones

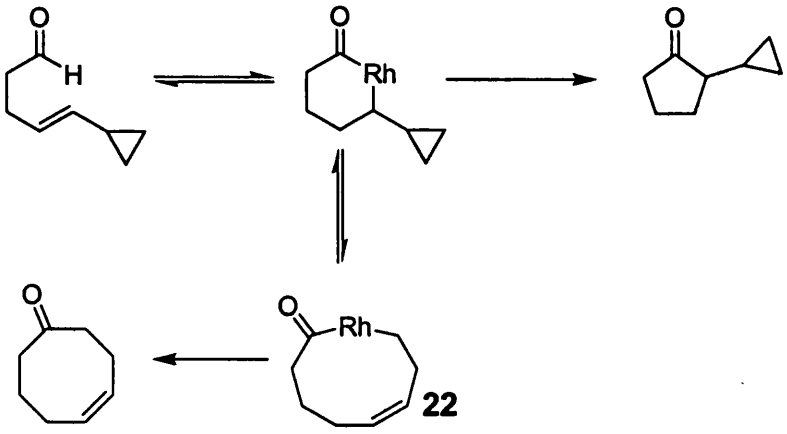
Shair *et al.* were able to synthesise eight-membered rings by incorporating a cyclopropane ring in the initial aldehyde. For example, 5-cyclopropyl-3-phenylpent-4-enal **20** has been successfully converted to 7-phenylcyclooct-4-enone **21** (scheme 12). Although the yields at this stage are moderate they are continuing work to extend the range of substrates and yields.[22]



20 **65% 21**

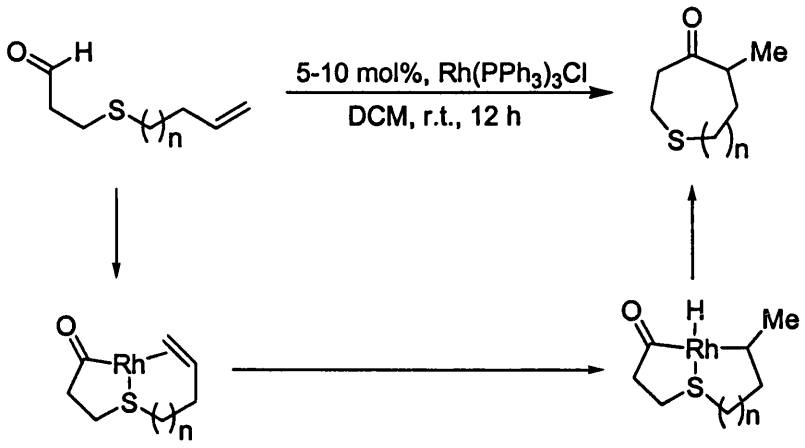
Scheme 12: Formation of 8-membered rings by Shair

The key aspect to their proposed mechanism is the fragmentation of the 6-membered rhodacycle into a ring expanded nine-membered rhodacycle **22**. This then undergoes reductive elimination to give the required cyclooctenone (scheme 13). The same synthesis with Wilkinson's complex was ineffective. In common with other work, ethylene saturation of the solvent gave an increase in yield presumably by decreasing any decarbonylation. Some coordinating solvents, such as tetrahydrofuran, inhibit the reaction almost completely, presumably due to the solvent coordinating to the cationic rhodium centre.



Scheme 13: Proposed mechanism of synthesis of cyclooctenones

With larger ring sizes, hydroacylation using chelation is a particularly valuable tool as it can direct the reaction to the desired product. Bendorf *et al.* have used a system employing sulfur as a "tether" atom.[28] Using this strategy they were able to give good results with 7- and 8- membered heterocycles, although larger ring sizes were unsuccessful. This relies on the formation of a chelation stabilised intermediate (scheme 14).



Scheme 14: Chelation-assisted intramolecular hydroacylation for the synthesis of sulfur heterocycles

They were able to react both alkene and alkyne containing substrates. Control experiments using an oxygen chelate indicated that the sulfur was required for chelation to be effective. This chelation approach is also used in intermolecular reactions with a good deal of success as outlined later.

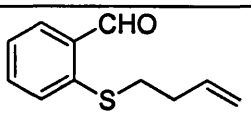
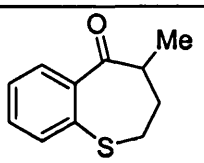
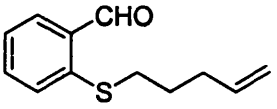
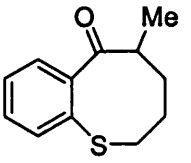
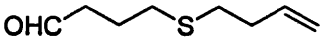
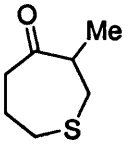
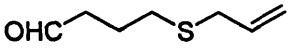
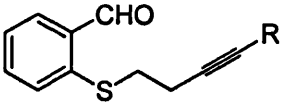
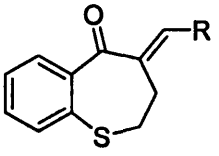
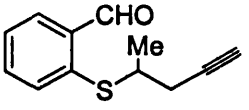
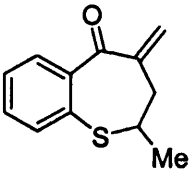
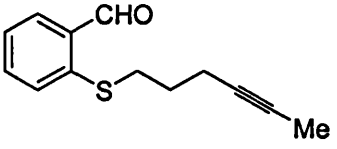
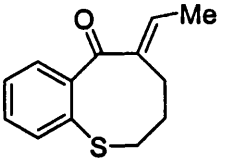
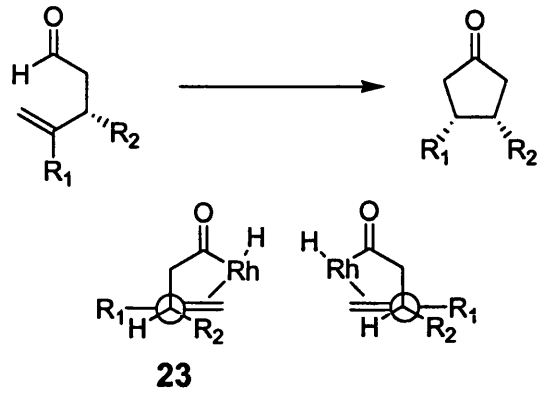
Entry	substrate	product	Yield (%)
1			92
2			62
3			82
4		N/A	0
5			R= H, 54 R=Me, 89
6			65
7			86

Table 3: Sulfur chelation approach to larger heterocycles

1.43 Asymmetric Catalysis

There has been a large amount of work on asymmetric intramolecular hydroacylation. Sakai was the first to study diastereoselective reactions involving 3,4-disubstituted 4-pentenals.[29] They attributed their resulting selectivity to allylic strain, leading to transition state **23** being favoured.

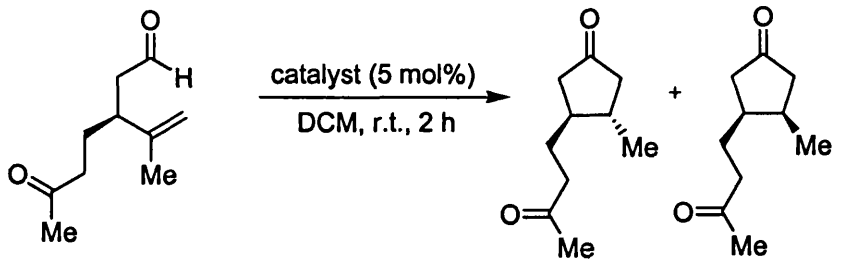


23

Scheme 15: Diastereoselective reaction of 3,4-disubstituted 4-pentenals

30 mol% catalyst loadings were needed for successful reaction, however a range of functional groups were tolerated including chloro-, hydroxyl, ketol and lactone groups forming only the *cis* diastereomers. This stereoselective cyclisation has been used in the diastereoselective synthesis of several natural products including prostaglandins.[30-32]

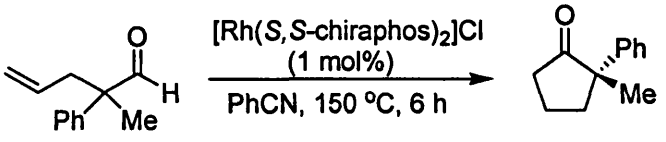
Diastereoselective reactions have since been extended with the use of chiral Rh(I) catalysts, also used for enantioselective reactions. Using Rh[BINAP]ClO_4 **25** Sakai was able to synthesise all four possible stereoisomers of 3,4-disubstituted cyclopentanones (table 4).[33] Although a neutral compound Rh[BINAP]Cl could be used, slightly lower selectivity was obtained and the catalyst loadings needed to be increased to 50 mol%.



entry	substrate	catalyst	time (h)	yield (%)	*cis:trans*
1	3*R*	Rh[(*S*)-BINAP]ClO_4	1.5	85	<1:>99
2	3S	Rh[(*R*)-BINAP]ClO_4	2	86	<1:>99
3	3*R*	Rh[(*R*)-BINAP]ClO_4	4	74	97:3
4	3*S*	Rh[(*S*)-BINAP]ClO_4	5	82	96:4

Table 4: Diastereoselective hydroacylation reactions

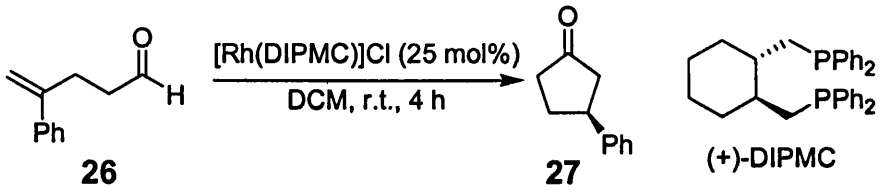
The first reported enantioselective reaction was by James, who used *bis*-chiral diphosphine rhodium(I) complexes to perform a kinetic resolution of chiral 4-pentenals. They were able to synthesise cyclopentanones from racemic pentenal with up to 69% *ee* (scheme 16).[34, 35]



Scheme 16: First enantioselective intramolecular hydroacylation

The enantioselectivity was only achieved at low conversions (17%) as at higher conversions of 50-60%, enantioselectivity only reached 40%. A very low catalyst loading was possible (1 mol%), however high temperatures of 150 °C were needed to allow the reaction to proceed.

Sakai was the first to achieve enantioselective reactions with achiral 4-pentenals. Rh(DIPMC)Cl proved to be the best catalyst, yielding the phenyl substituted cyclopentanone **27** in 71% yield and 76% *ee* from 4-phenylpentenal **26**.[36, 37]

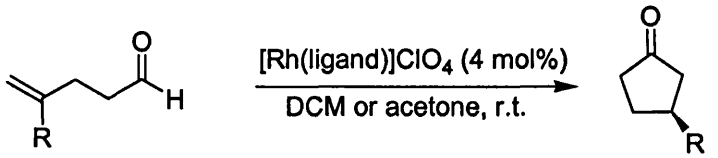


26 27

Scheme 17: Enantioselective intramolecular hydroacylation

Sakai extended this work reporting good to excellent enantioselectivities for the hydroacylation of 4-pentenals to chiral cyclopentanones using $[Rh(BINAP)]ClO_4$.[38]

Bosnich has also investigated this area using [Rh (chiral diphosphine)]$^+$ catalysts with successful early results.[39, 40] The group was able to synthesise a range of products with *ee's* of 87% or above, using BINAP **28**, Me-DuPhos **29** or chiraphos **30** as ligand.[41] The most successful ligand for the reaction depended on the exact substrate being used. BINAP appeared to be the most successful for substrates with tertiary or ester ketone components while DuPhos was the more effective for aldehydes with primary or secondary alkyl groups, with which they were able to report systems giving 93-94% *ee* at 25 °C.[42, 43] BINAP was reported to be less successful with substrates containing a phenyl ring (ee of 70-75%) and these results were slightly improved by the use of chiraphos as the ligand.[44] Despite the group's previous work on the mechanism showing that apart from the reductive elimination all the steps are reversible the *ee* values remained high.[45] They cannot identify one step responsible for this but it seems that a mix of rate constants controls the enantioselectivity.



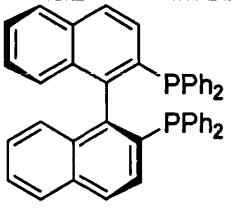
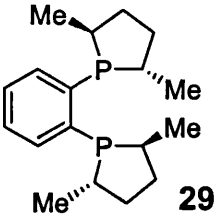
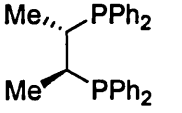
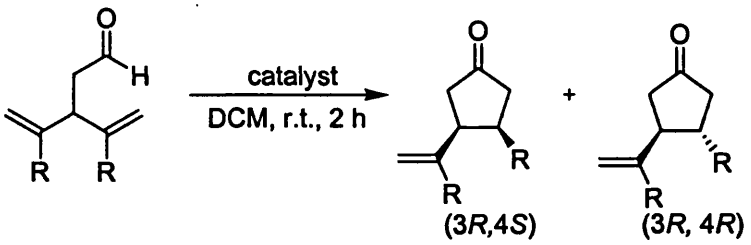
entry	substrate, R =	Ligand	*ee* (major product) (%)
1	*t*-Bu		>99
2	$SiMe_3$		>99
3	CO_2Et		>99
4	C(O)Me		87
5	C(O)Ph	*(S)*- BINAP **28**	94
6	Me		94
7	Bu		94
8	*i*-Pr		94
9	cyclohexyl		93
		(S,S,)-MeDuphos **29**	
10	Ph		70
11	4-MeO-Ph		75
		(S,S)-chiraphos **30**	

Table 5: Representative results of asymmetric cyclisation of 4-substituted pentenal

Desymmetrisation reactions have also been performed with a hydroacylation reaction, leading to the formation of two stereocentres by the groups of Sakai and Suemune.[33,46]

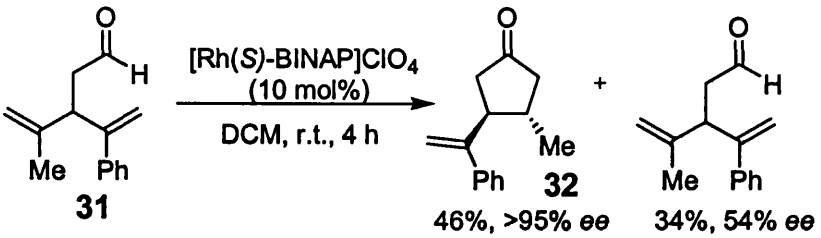


entry	R	catalyst	time (h)	yield (%)	*cis:trans*	*ee* (%)	config.
1	Me	Rh[(*R*)-BINAP]Cl	72	25	93:3	>95	3*S*, 4*R*
2	Me	Rh[(*R*)-BINAP]Cl	72	31	97:3	>95	3*R*, 4*S*
3	Me	Rh[(*R*)-BINAP]ClO_4	1	81	3:97	>95	3*S*, 4*S*
4	Me	Rh[(*S*)-BINAP]ClO_4	1	84	4:96	>95	3*R*, 4*R*
5	Ph	Rh[(*S*)-BINAP]ClO_4	2	70	18:82	>95	3*S*, 4*S*
6	Ph	Rh[(*R*)-BINAP]ClO_4	2	76	17:83	>95	3*R*, 4*R*
7	*i*-Bu	Rh[(*R*)-BINAP]ClO_4	3	74	2:98	>95	3*S*, 4*S*
8	*i*-Bu	Rh[(*S*)-BINAP]ClO_4	4	77	2:98	>95	3*R*, 4*R*

Table 6: Desymmetrisation using hydroacylation methodology

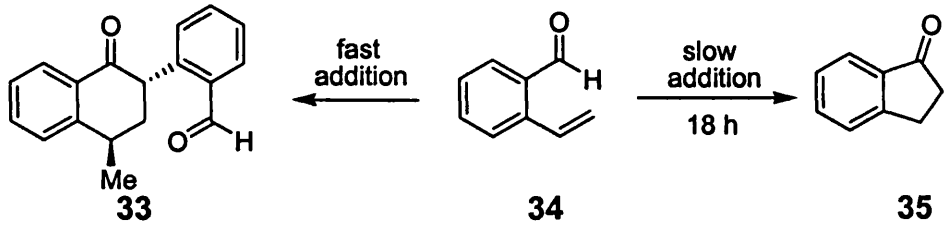
Symmetrical 3,3,4-trisubstituted aldehydes have been used in this methodology to yield trisubstituted cyclopentanones with a quaternary carbon. These reactions gave *trans*-cyclopentanones with excellent enantioselectivity although the neutral catalysts did not give good results.[33,47]

The same group reported the kinetic resolution of dissymmetric racemic diene-aldehydes where it was possible to choose the *trans* or *cis* product by the correct choice of catalyst. Starting from racemic 4-methylphenylvinylpentenal **31** methylphenylvinylcyclopentanone **32** and enantiomerically enriched methylphenylvinylpentenal could be synthesised selectively. Cationic complexes lead to the *trans* product using only 5 mol% catalyst while the neutral complex gave the *cis* complex although a 50 mol% catalyst loading was required for reaction with these systems (scheme 18).[48]



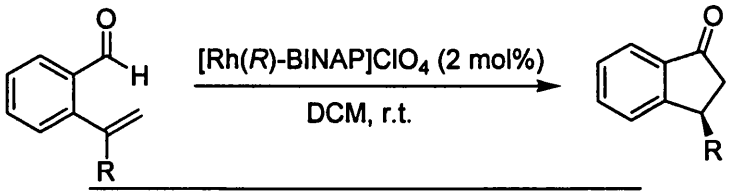
Scheme 18: Kinetic resolution of dissymmetric racemic diene-aldehydes

The Morehead group have developed an effective synthesis to 3-substituted indanones **35** using hydroacylation.[49] For this reaction they reported it was necessary to add the substrate **34** slowly over 18 hours to avoid the appearance of a dimer **33**, which under quicker addition protocols becomes the major product.



Scheme 19: Synthesis of indanones or dimer dependant on speed of addition

Variation of the R group can be tolerated within the reaction at low catalyst loadings (2 mol%) giving excellent enantioselectivity in all examples except a trimethylsilyl substituent (entry 6, table 7).[49]

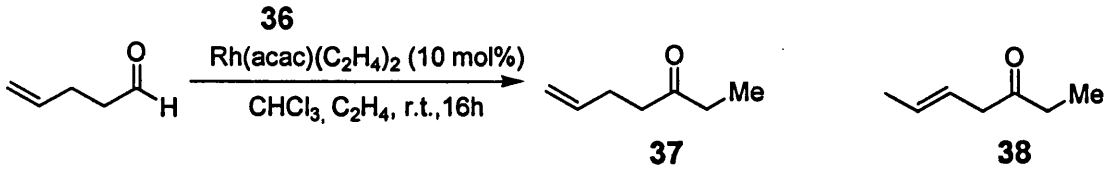


entry	substrate (R)	yield (%)	*ee* (%)
1	Me	97	99
2	Et	97	99
3	Ph	98	98
4	2-Naph	88	96
5	CH_2CH_2OH	97	96
6	$SiMe_3$	93	70
7	CF_3	90	99
8	COOEt	89	96

Table 7: Enantioselective synthesis of Indanones

1.5 Intermolecular Hydroacylation

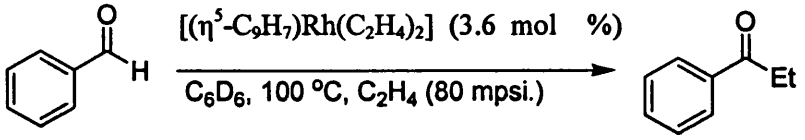
There are relatively few examples of intermolecular hydroacylation as the problems of decarbonylation are emphasized in the intermolecular process. Extending the reaction to include intermolecular systems is in theory, a very attractive process as the products would not be limited to cyclic materials. This would allow the production of acyclic ketones in an atom economic process. One of the major drawbacks of intermolecular hydroacylation is the fact that harsh conditions are often needed to suppress decarbonylation and hence degradation of the catalyst. Miller's early work on intramolecular hydroacylation using $RhCl(PPh_3)_3$ showed that decarbonylation was reduced when the reactions were carried out in saturated ethylene; which was due to the vacant site on the rhodium being filled with the ethylene and so preventing decarbonylation. They were able to extend this work to actually promote intermolecular reactions by using a different catalyst,- $Rh(acac)(C_2H_4)_2$, **36** which gave heptanones **37** and **38** while cyclopentanone was only detected in 1% yield (scheme 20).[14]



Scheme 20: Intermolecular hydroacylation of ethylene

This system is quite limited as it requires unsaturation to be at the aldehyde 4 – position. This is thought to be because it forms a chelated intermediate with alkene coordination stabilising the Rh-acyl intermediate. No saturated aldehydes reacted to give hydroacylation products, which is a serious limitation of this reaction.

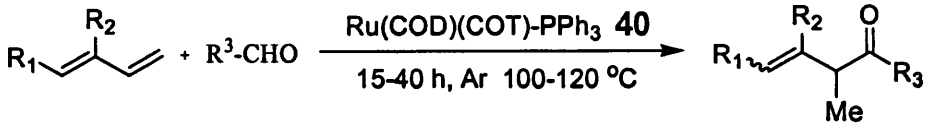
Marder and Milstein extended the range of substrates when they discovered that aromatic aldehydes could undergo hydroacylation with ethylene using a rhodium indenyl complex ($[(\eta^5\text{-}C_9H_7)Rh)C_2H_4)_2]$ **39**). For this process high pressures of ethylene were required although this did inhibit decarbonylation and formation of metallic rhodium.[50]



Scheme 21: Intermolecular hydroacylation with ethylene

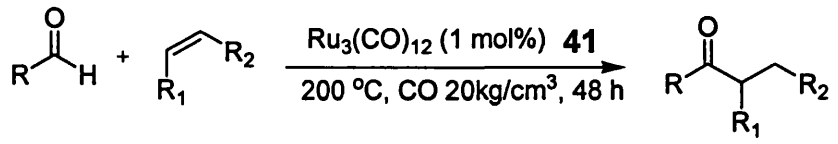
1.51 Catalysts used for intermolecular hydroacylation

Rhodium is not the only metal that has been successfully used in intermolecular hydroacylation and there are examples using cobalt[51-54] and ruthenium.[55-58]



Scheme 22: Example of ruthenium catalysed hydroacylation

Watanabe and Kondo have used low loadings of $Ru_3(CO)_{12}$ (1 mol%) **41** with a high pressure of CO and high temperature to react aromatic and heteroaromatic aldehydes with a range of alkenes.[57] Simple cyclic and non-cyclic alkenes could be employed to gain hydroacylation products in moderate yields with the catalyst $Ru_3(CO)_{12}$ (table 8). Aliphatic aldehydes led to the formation of transformylation products, e.g. the reaction of heptanal with cyclohexene gave cyclohexanecarboxaldehyde instead of the expected hydroacylation products. With a catalytic system of $[Ru(COD)(COT)PPh_3]$ **40** aromatic aldehydes could be added to dienes to generate unsaturated ketones (scheme 22). This system again did not require a CO atmosphere.



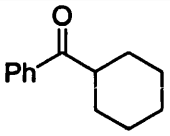
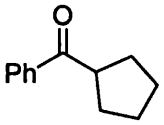
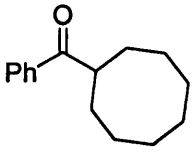
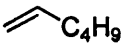
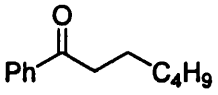
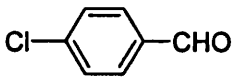
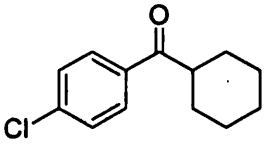
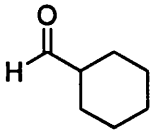
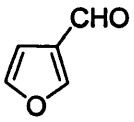
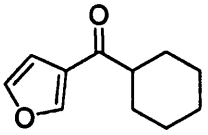
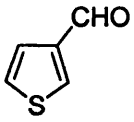
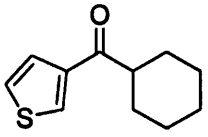
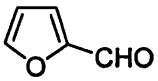
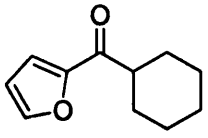
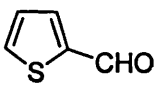
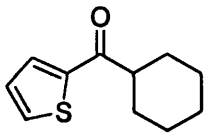
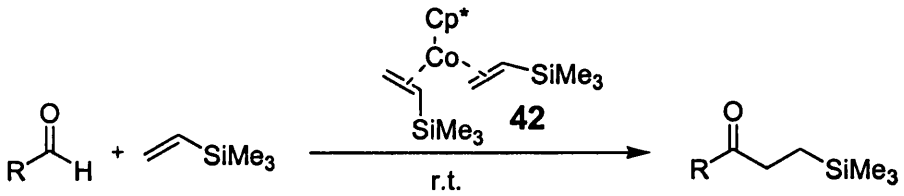
entry	aldehyde	alkene	product	yield (%)
1				44
2				47
3				12
4				35
5				48
6	$(HCHO)_n$			15
7				27
8				30
9				25
10				41

Table 8: Ruthenium catalysed intermolecular hydroacylation

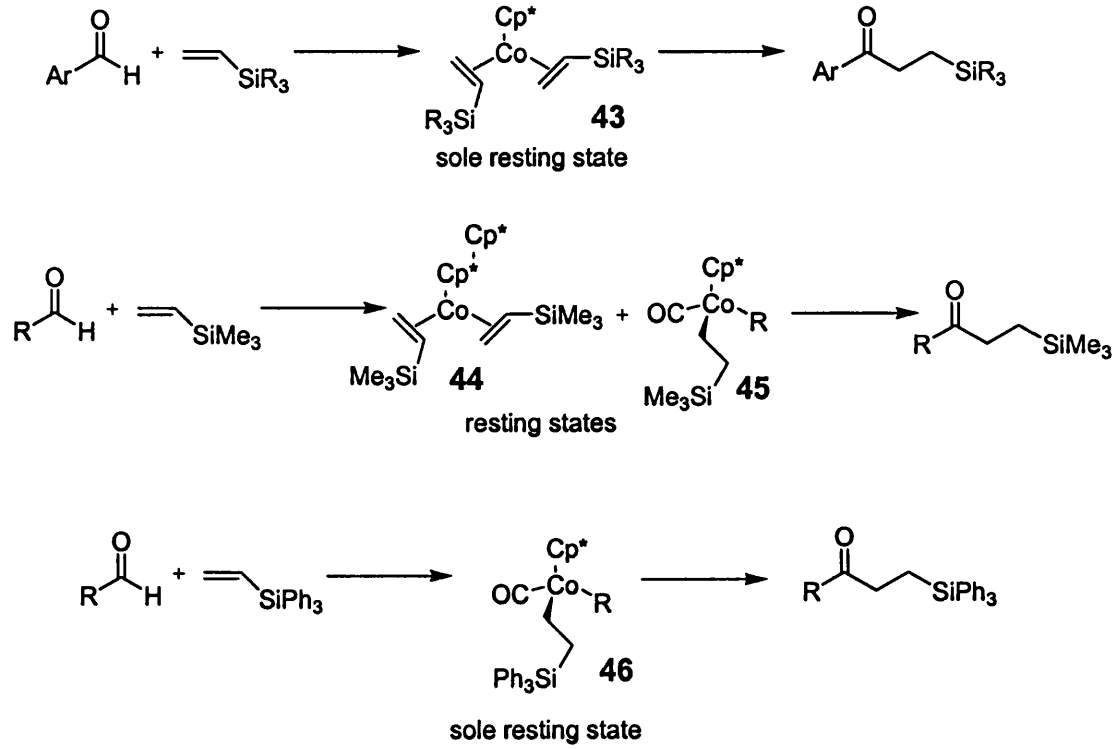
Cobalt complexes has been developed as hydroacylation catalysts by the Brookhart group.[53] Co(I)-bisolefin complex **42** has been used for the addition of aromatic and aliphatic aldehydes to vinyltrialkylsilanes. This is a particularly good system as a large range of aldehydes are able to be employed in the reaction with low catalyst loadings (0.5 mol%), at room temperature. This system is however limited to vinylsilanes, including vinyltriphenylsilane and vinyltrimethoxysilane. The latter has a much slower reaction rate but goes to completion with 1 mol% catalyst. This is probably due to the relative binding affinities of the olefins to the Co(I) centre.



entry	aldehyde (R)	conversion (%)
1	4-Me_2N-C_6H_4	100
2	4-MeO-C_6H_4	100
3	4-Me-C_6H_4	77
4	3,4-$(MeO)_2$-C_6H_3	30
5	3,4,5-$(MeO)_3$-C_6H_2	35
6	3-Me-C_6H_4	19
7	Ph	8
8	Et	98
9	Pr	97
10	*i*Bu	99
11	2-Ph-Pr	75
12	Neopent	98
13	*i*Pr	98
14	Cy	99
15	*t*Bu	12

Table 9: Cobalt catalysed intermolecular hydroacylation

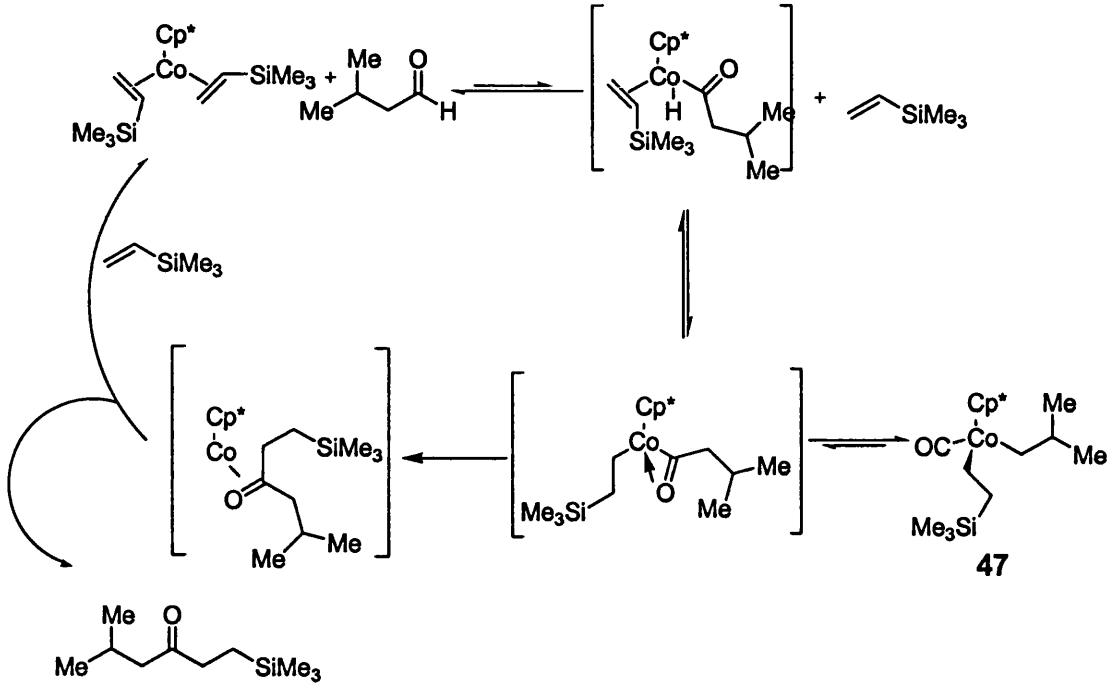
Investigations, by the Brookhart group, have shown that the nature of the aldehyde has a huge effect on the resting state of the catalyst. Aromatic aldehydes with electron-donating substituents give high turnover numbers and yields. Aromatic aldehydes with less electron-withdrawing groups lead to significantly reduced catalyst lifetimes due to decarbonylation and catalyst deactivation. However, it was reported that the initial rates are unaffected. The group went on to report the reaction of aliphatic aldehydes, where significant differences were found. They reported that the nature of the catalyst resting state was carefully balanced by the binding affinity of the olefin and the reactivity of the aldehyde. Aromatic aldehydes give rise to a resting state solely comprised of complex **43**, while aliphatic aldehydes are in equilibrium between complex **44** and **45**. Using a more bulky olefin makes complex **43** unfavoured leading to solely complex **46** acting as the resting state.



Scheme 23: Resting states during catalytic hydroacylation using cobalt (I) [54]

Further studies indicated that the rate determining step of the process was the reductive elimination step so any isomerisation must occur before this. The same conclusions that were proposed by Bosnich were also reached by the Brookhart group as they reported all the steps prior to reductive elimination are reversible and this can lead to the formation of isomerised products and aldehydes e.g. butyraldehyde to *iso*butyraldehyde observed with alkyl aldehydes.

Mechanistic studies have been undertaken by the same group to understand the process further. These studies have given rise to the mechanism outlined in scheme 24.

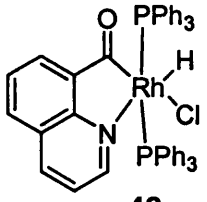


Scheme 24: Mechanism for intermolecular hydroacylation with Co(I) complex[54]

The mechanism shown in scheme 24 is the same for aromatic aldehydes except intermediate **47** is not observed.

1.52 Chelation assisted hydroacylation

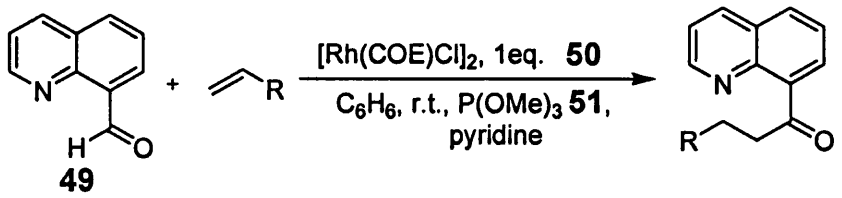
A chelation approach to intermolecular hydroacylation has been investigated by many groups and has been used extensively. The first intermolecular reactions by Miller who used enals attributed their success to chelation from the alkene group. Heteroatoms were a natural extension to this and initially aldehydes with coordinating nitrogen or phosphine groups were used as chelating options.[59, 60] For example quinoline-8-carboxaldehyde was used by Suggs who was able to isolate complex **48** from its reaction with Wilkinson's complex.[61-63]



48

Figure 5: Complex isolated from the reaction of Wilkinson's complex and quinoline-8-carboxaldehyde

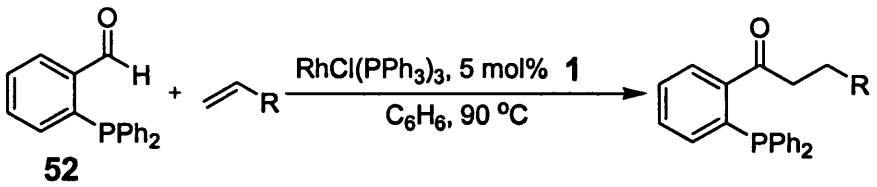
Following the addition of $AgBF_4$ and octene the hydroacylation product could be isolated.[64] Changing Wilkinson's complex to $[RhCl(COE)]_2$ **50** and trimethyl phosphite **51** enabled a range of alkenes to be used in this process. A major drawback to this work was the requirement of stoichiometric amounts of rhodium; lowering the catalyst loadings to 10 mol% resulted in much reduced yields e.g. aldehyde **49** with styrene only gave 13% yield of product with 10 mol% catalyst compared to yields of 54-75% with 50 mol% catalyst.



49

Scheme 25: Intermolecular hydroacylation of quinoline-8-carboxaldehyde

In the same manner *o*-diphenylphosphino benzaldehyde **52** can be combined with a range of neutral alkenes using Wilkinson's complex **1**.[60, 65]

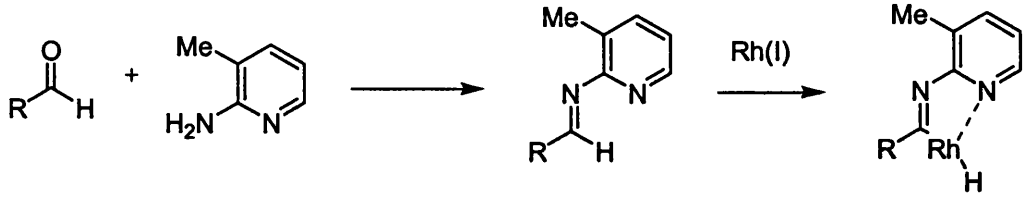


52

Scheme 26: Hydroacylation of *o*-diphenylphosphino benzaldehyde

These examples give good indications of the kinds of stabilisation needed to effect reaction but they are severely limited as they require quinoline or phosphine in the starting materials which then inevitably become incorporated into the final products.

The extent of chelation stabilised hydroacylation was greatly increased by utilising picolylimines successfully in the reaction.

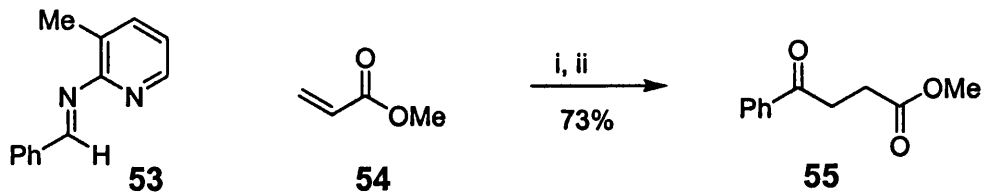


Scheme 27: Formation of picolyl imine and subsequent coordination to Rhodium

The 1,5-relationship between the coordinating group of the imine and the aldimine C-H allows coordination to occur with the rhodium being "held" in the correct place for C-H activation (scheme 27). This stops decarbonylation from occurring and forms a 5-membered chelated metal system.

The picoline group can easily be removed by hydrolysis yielding ketonic products. Some of the first work done on this area was by Suggs *et al.* who used a system with a phenyl aldimine under ethylene pressure. Using stoichiometric amounts of rhodium catalyst, propiophenone was formed in 85% yield. Using 5 mol% catalyst gave the product in 45% yield. This system has now been developed further by Jun being applied to the synthesis of ^{18}F labelled ketones.[66]

Previous work from our laboratory has shown that a picolyl imine system can be used to form 1,4-dicarbonyl products *via* hydroacylation of acrylates. For example methyl acrylate **54** could be successfully reacted with benzylidene-3-methylpyridinimine **53** to yield methyl 4-oxo-4-phenylbutanoate **55** (scheme 19).[67]

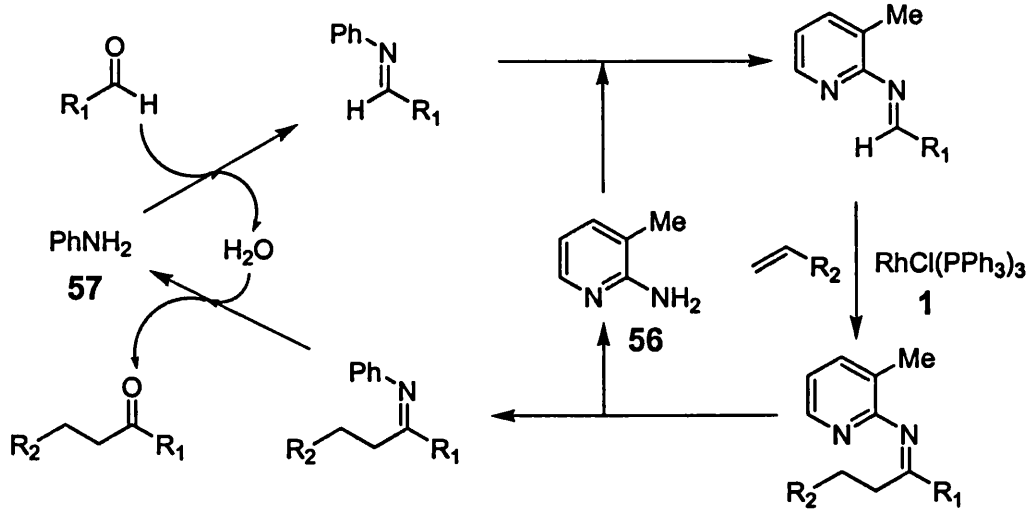


i) $RhCl(PPh_3)_3$ (5 mol%), THF, 135 °C, 8 h; ii) HCl (aq.)

Scheme 28: Formation of 1,4-dicarbonyl products from hydroacylation of acrylate derivatives.[68]

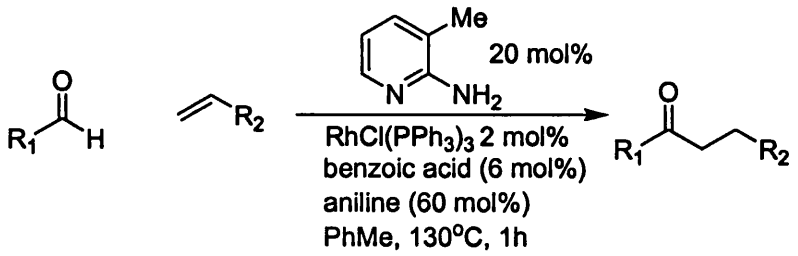
Although this system works well with unsubstituted acrylates further substitution in the α and β positions on the alkene leads to much reduced yields, in addition only aromatic aldehydes are currently successful. It was found that adding electron withdrawing groups on the phenyl group lead to much faster reaction times, although the yield was the same in both cases. The reaction time can also be dramatically decreased through the use of microwave techniques, from eight hours to ten minutes.[69]

Jun has made significant progress within intermolecular hydroacylation by using a chelation approach with 2-amino-3-picoline **56**.[70, 71] *In-situ* formation of the picolyl imines from the corresponding aldehyde has allowed the reaction of a varied range of alkenes and aldehydes in good yield (scheme 29). A complex mixture was used to create the imines: picolylamine (20 mol%) **56**, benzoic acid (6 mol%) and aniline (60 mol%) **57** with Wilkinson's complex (2 mol%) **1** in toluene at 130 °C.



Scheme 29: Proposed mechanism of picolylamine in hydroacylation reaction[71]

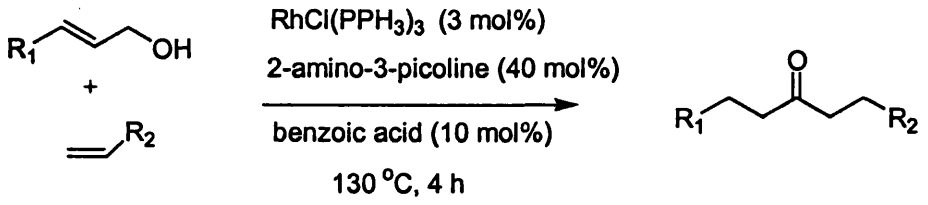
Relatively high loadings (20-40 mol%) of 2-amino-3-picoline **56** and high temperatures are generally required for these reactions. The system is also mainly limited to aromatic aldehydes.[72] Despite these drawbacks, low catalyst loadings of rhodium are routinely used and a variety of aromatic aldehydes and alkenes have been successfully employed.[73]



entry	R_1	R_2	yield (%)
1	Ph	*n*-Bu	98
2	Ph	*n*-Pr	83
3	Ph	*n*-Hex	99
4	Ph	*t*-Bu	84
5	Ph	$SiMe_3$	95
6	Ph	C_6F_5	98
7	Ph	$PhOCH_2$	95
8	4-MeO-C_6H_4	*n*-Bu	79
9	4-CF_3-OC_6H_4	*n*-Bu	71
10	4-Me_2N-C_6H_4	*n*-Bu	60
11	4-Ph-C_6H_4	*n*-Bu	95
12	$PhCH_2CH_2$	*n*-Bu	71

Table 10: 2-aminopicoline as chelating agent

The R_1 groups on the aldehyde were limited to phenyl or cyclohexane based functionality while the R groups on the alkene were mainly alkyl (table 10). Yields of between 60-99% were achieved. High temperatures are needed, however the Rh catalyst loadings are low. Advances have also been made with the use of microwave technology and Montmorillonite K10 clay as a co-catalyst to aid imine formation. They have further extended this work to include the production of aliphatic ketones from allylic alcohols (table 11). Again the reported R groups are generally aliphatic or aromatic in nature but the isolated yields are between 78-92% and again catalyst loadings are low.[65, 74, 75]



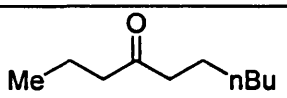
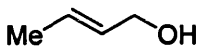
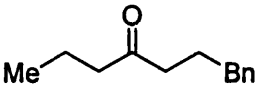
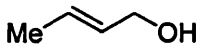
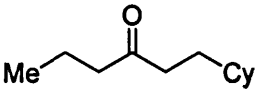
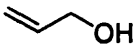
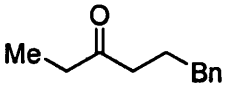
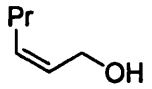
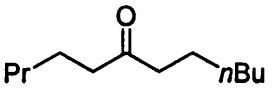
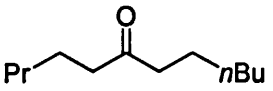
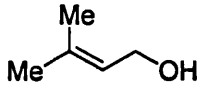
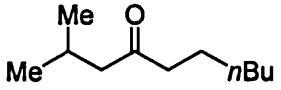
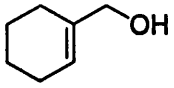
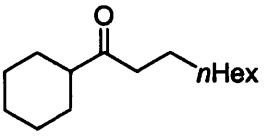
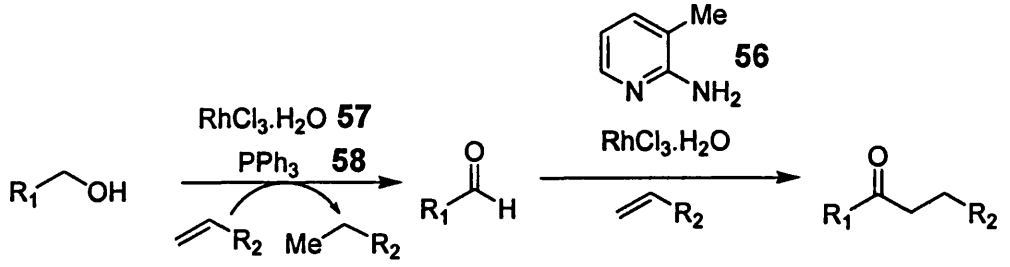
entry	alcohol	R_2	product	yield (%)
1		*n*Bu		91
2		Bn		78
3		Cy		83
4		Bn		77
5		*n*Bu		92
6		*n*Bu		85
7		*n*Bu		63
8		*n*Hex		64

Table 11: Aliphatic alcohols in hydroacylation reactions

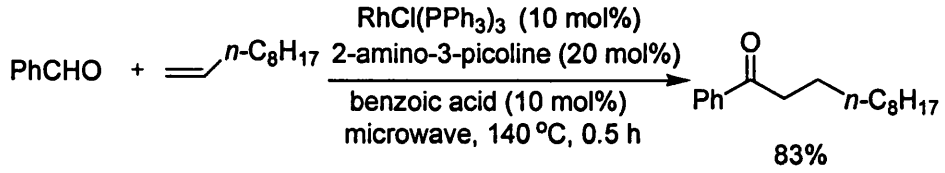
Primary alcohols have also been used as aldehyde precursors.[74] The rhodium catalyst oxidises the alcohol to the aldehyde before promoting the hydroacylation reaction. The oxidant for the system is an extra equivalent of the alkene.



Scheme 30: Primary alcohol as aldehyde precursor in hydroacylation reaction

For this system it was found that Wilkinson's complex is not the optimal catalyst option, instead $RhCl_3.H_2O$ **57** with triphenylphosphine **58** and stoichiometric picolylamine **56** was the most effective combination (scheme 30). They were able to modify the system to accept primary amines as the aldehyde equivalents.

In conjunction with Loupy a solvent free system has also been developed. This requires microwave conditions for an effective reaction but allowed the same reactions to be carried out in much reduced time scales, no solvents and with similar yields.[76, 77]



Scheme 31: Solvent-free hydroacylation under microwave irradiation[78]

Salicylaldehyde **59** has also been used as a chelating substrate (figure 6). Murai *et. al.* used this aldehyde with a range of alkenes with limited success. Although most alkenes were not very successful in the reaction vinyltriethylsilane **60** was an exception with good results obtained. Equally they were able to use simple allenes in the reaction (scheme 32).[79]

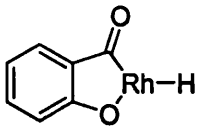
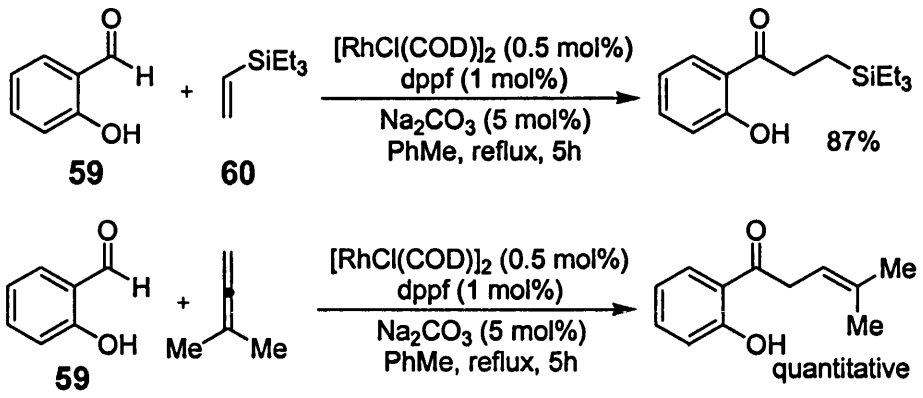
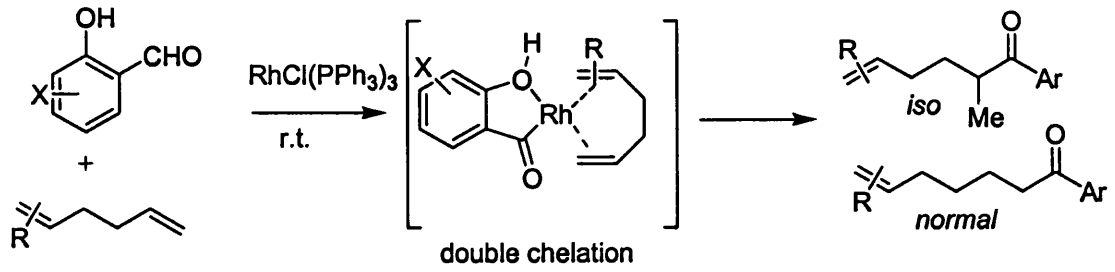


Figure 6: Chelation of salicylaldehyde



Scheme 32: Vinyltriethylsilane and allene with salicylaldehyde

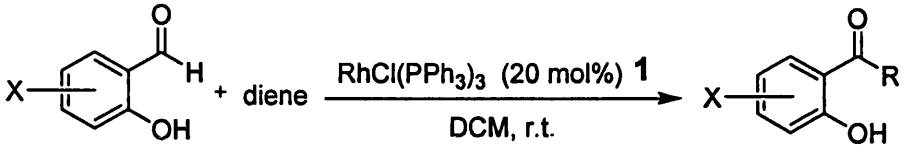
Salicylaldehyde **59** has also been used by Tanaka and Suemune *et al.*, who showed that a double chelation strategy is effective at allowing intermolecular hydroacylation under mild conditions using dienes.[80, 81] Previous work done by the group on the cyclisations of 4-pentenals did not allow the extension of the work into intermolecular systems. Similarly when they turned to salicylaldehyde they were unable to get simple alkenes, e.g. octene, to work effectively, however using a double chelation strategy from a diene and aldehyde allowed reaction under surprisingly mild conditions (scheme 33). Deuterium labelling studies carried out by the group showed considerable deuterium scrambling, which is common to other deuterium work done in hydroacylation reactions. They proposed a mechanism involving chelation from both points of the aldehyde and diene to account for the high reactivity.



Scheme 33: Double-chelation-assisted intermolecular hydroacylation

Using low catalyst loadings of Wilkinson's complex **1** a range of substituted salicylaldehydes were reacted with 1,4-penta- and 1,5-hexadienes to give excellent yields of hydroacylation products. They were able to introduce further functionality at one end of the diene although in all cases this led to the other terminus of the diene

being hydroacylated. There was selectivity in favour of the branched product although this was only moderate (60-77%) (table 12).



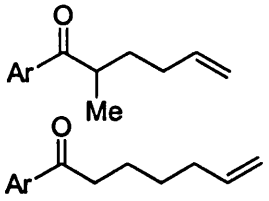
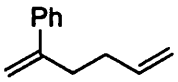
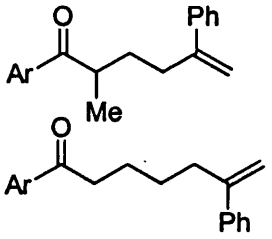
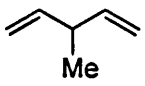
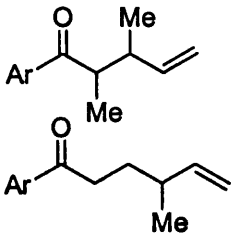
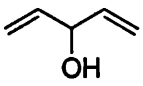
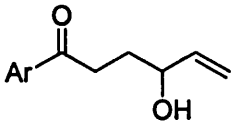
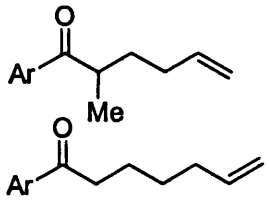
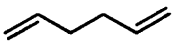
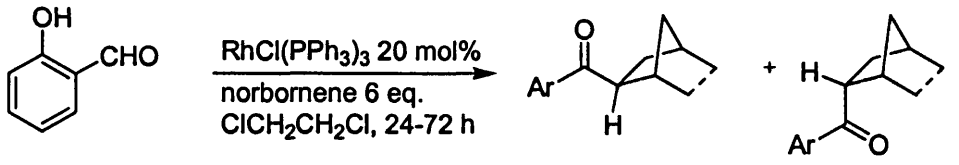
entry	aldehyde (X)	diene	products	yield (%)	ratio b:l
1	H			100	4:1
2	H			77	6:1
3	H			91	3:5
4	H			93	n/a
5	4-OH			90	3:1
6	4-Me			42	3:1
7	4-Cl			100	4:1
8	4-NO_2			73	2:1
9	2-Me			71	5:1
10	2-OH			58	3:1
11	3-OH			75	4:1

Table 12: Salicylaldehyde reaction with dienes

The group investigated the effect of solvent, the addition of bases and other rhodium sources to see if any advantages could be gained. In general chlorinated solvents or ethanol proved effective with the best combination proving to be 5% EtOH in DCM. Adding a base such as Na_2CO_3, NaOAc or CsF was reported to accelerate the reaction which they attribute to the deprotonation of the phenolic hydrogen. The addition of AgOTf or $AgClO_4$ equally accelerated the reaction rate, although this is presumably due to the formation of a cationic rhodium species. The Bosnich catalytic system of $[Rh(dppe)]ClO_4$ **12** was also tried although this resulted in a much slower reaction.[80]

The same group has managed to effect hydroacylation between norbornenes and salicylaldehyde.[82] The Miura group had earlier reported the hydroacylation of norbornylene with salicylaldehyde with $[Rh(COD)Cl]_2$ however they were only able to isolate 6-39% yield.[83] Tanaka was able to improve this considerably and gain largely the *exo*-product by using a similar system to the double chelation strategy (table 13).



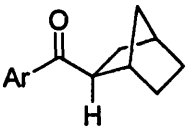
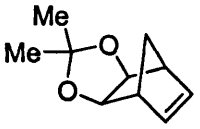
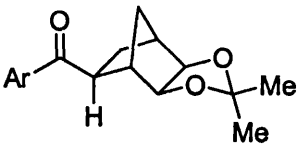
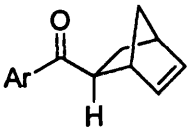
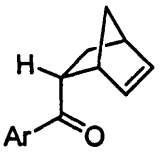
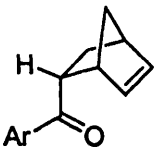
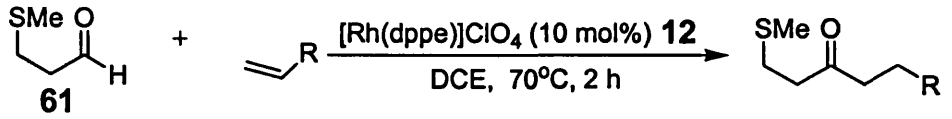
entry	norbornene	additive	product (%)	yield (ratio *endo:exo*)
1		-		>99 (>1:99)
2		-		36 (>1:99)
3		-		16 (5:1)
4		K_2CO_3		>99 (20:1)
5		K_3PO_4		>99 (>25:1)

Table 13: Reaction of salicylaldehyde with norbornenes

Previous work from the Willis group has identified sulfur chelation-assisted hydroacylation as a successful strategy in intermolecular hydroacylation.[84] A range of products were synthesised using 3-methylsulfanyl propionaldehyde **61** reacted with different olefins, utilising $[Rh(dppe)]^+$ **12** generated *in situ* from the catalyst precursor $[Rh(NBD)(dppe)]ClO_4$.[23] Unfortunately with these substrates no further substitution on the alkene at either the α or β position could be tolerated reducing the variation of the reaction. This initial work was limited to the single aldehyde.



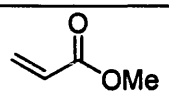
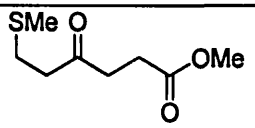
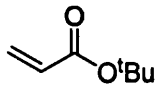
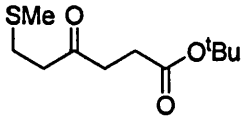
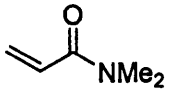
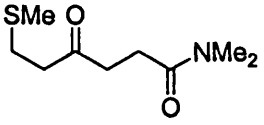
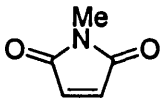
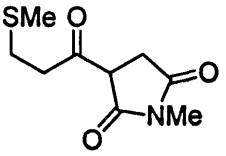
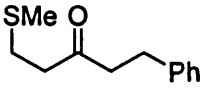
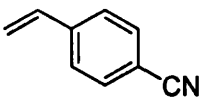
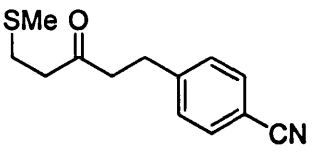
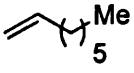
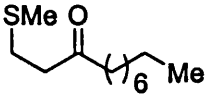
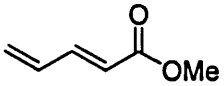
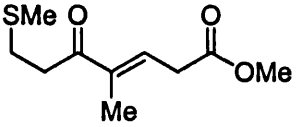
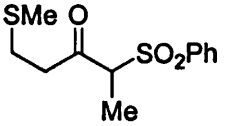
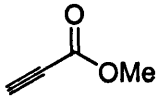
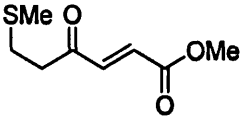
entry	alkene	Product	ratio linear:branched	yield (%)
1			4:1	71
2			5:1	81
3			>20:1	82
4			n/a	73
5			>20:1	41
6			>20:1	66
7			>20:1	33
8			>20:1	45
9			>20:1	84
10			10:1	82

Table 14: Hydroacylation of 3-methylsulfanyl propionaldehyde with representative alkenes

Electron-poor alkenes proved to be the most successful olefins, reacting to give a mixture of branched and linear ketones. In particular this has been a successful method for the production of 1,4-dicarbonyls, which are traditionally difficult substrates to synthesize despite their importance in many natural product synthetic routes and in heterocyclic synthesis (table 14).

1.6 Hydroacylation of alkynes

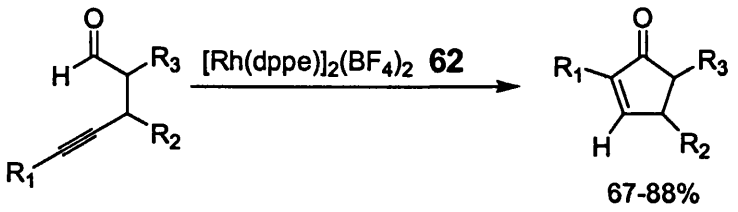
Hydroacylation of alkynes is slightly more complicated than with alkenes as there are 3 different isomers of alpha-beta-enones (branched, linear *E*- and linear *Z*-) that can be formed (scheme 34).

branched *α-β*-enone | *E*- *α-β*-enone | Z- *α-β*-enone

Scheme 34: Possible products of alkyne hydroacylation

There are relatively few examples of hydroacylation with alkynes although many advances have been recently made.

Fu *et al.* have made significant advances in the intramolecular hydroacylation for the synthesis of five membered rings with alkynes. They demonstrated the synthesis of a large number of cyclopentanones with varying functionalities employing $[Rh(dppe)]_2(BF_4)_2$ **62** as the catalyst (scheme 20). This reaction proceeded through an unusual *trans*-addition of the rhodium hydride to the alkyne.[24, 25]



R= alkyl, 5-aryl, 5-alkenyl and 5-alkynyl-substituted

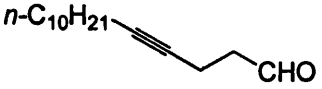
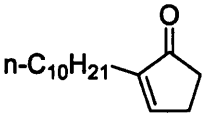
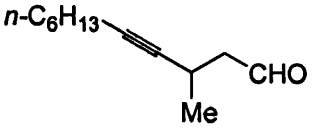
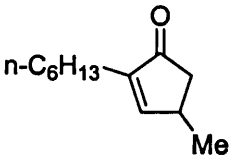
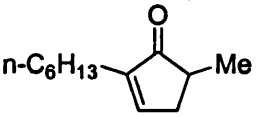
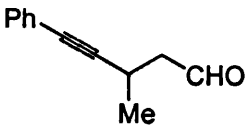
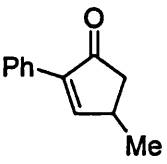
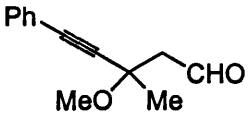
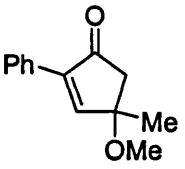
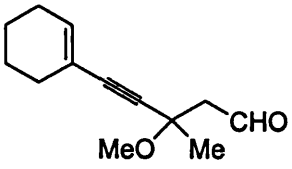
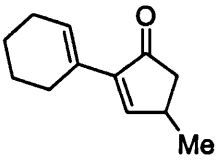
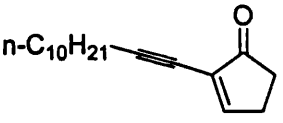
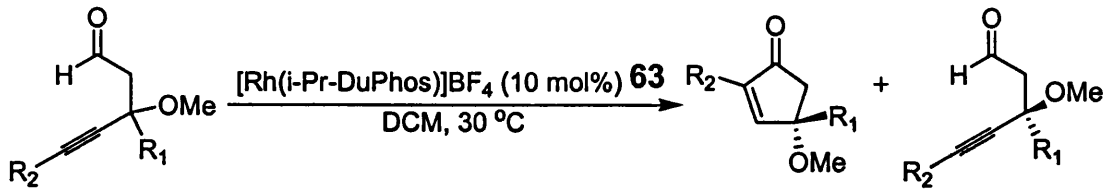
entry	substrate	product	yield (%)
1			67
2			75
3			67
4			88
5			75
6			84
7			76

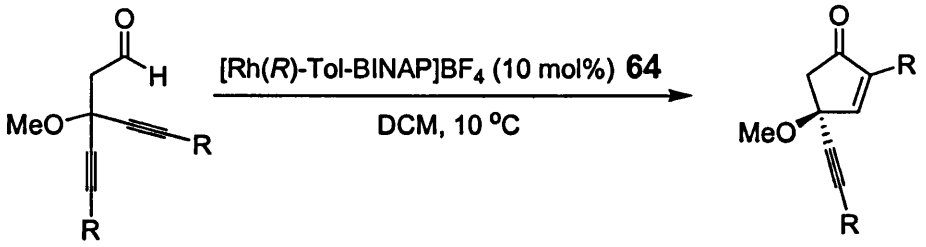
Table 15: Alkyne hydroacylation to cyclopentanones

As no sp^3 centre is formed in these reactions it is not possible to do enantioselective operations. The group was therefore able to extend this work by using the reaction for kinetic resolutions and desymmetrisation reactions. Using a Rh/(*i*-Pr-DuPhos) catalyst **63** they were able to achieve resolution with selectivity factors of 20-40. Both the unreacted starting material and cyclised product could be obtained with high *ee*. [85]



Scheme 35: Kinetic resolution *via* a hydroacylation reaction

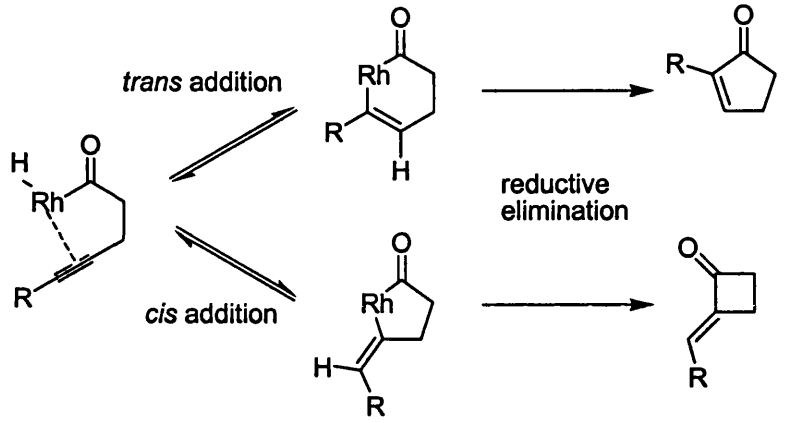
Within the desymmetrisation reactions achiral substrates with quaternary centres were used with Tol-BINAP catalysts **64** to give a range of enantiomerically enriched cyclopentenones, obtained with high levels of selectivity and yield.[85]



entry	R	yield (%)	ee (%)
1	*n*-C_5H_{11}	95	92
2	Cy	94	95
3	$(CH_2)_3Cl$	91	91
4	CH_2OMe	93	82

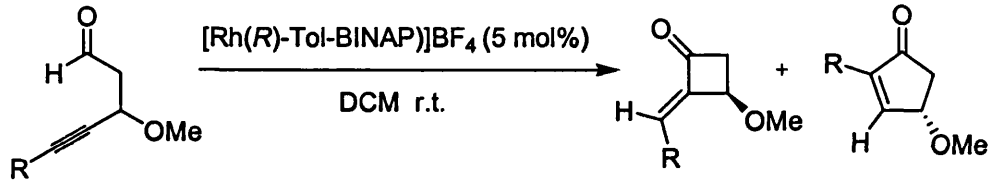
Table 16: Desymmetrisation reaction with alkynes

They have additionally been able to apply the same methodology, with a different ligand, to undergo a rare parallel kinetic resolution, forming cyclopentenone and cyclobutenone both in reasonable enantiomeric excess (84->99% *ee* cyclobutenone, 46-88 % *ee* cyclopentenone).[86] It was possible to choose which of these products is produced when starting with enantiopure *(S)* material by changing the ligand on the catalyst. *(S)*-Tol-BINAP **64a** gives cyclobutenone and *(R)*-Tol-BINAP **64b** gives cyclopentenone (scheme 36). They proposed that the different products come from different modes of addition of the rhodium hydride across the alkyne. The cyclobutenone comes from *cis* addition while the cyclopentenone is formed from the *trans* addition.



Scheme 36: Different modes of addition of the rhodium hydride

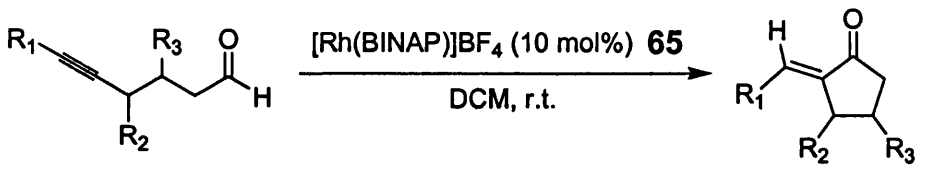
A range of aryl, hetero aryl and alkyl groups were successfully reacted in the 5-position (table 17). It was necessary to maintain a 3-methoxy group, however, to allow the parallel kinetic resolution to occur.



entry	R	cyclobutenone		Cyclopentenone	
		ee (%)	yield (%)	*ee* (%)	yield (%)
1	Ph	84	47	88	45
2	4-MeO(C_6H_4)	81	43	81	36
3	4-CF_3(C_6H_4)	>99	32	62	58
4	*o*-tol	>99	27	85	41
5	2-furyl	98	26	46	66
6	Cy	>99	25	84	41

Table 17: Parallel kinetic resolution *via* a hydroacylation reaction

Tanaka has used complimentary methodology to the Fu chemistry reporting the treatment of a range of 5-alkynals with [Rh(BINAP)]BF_4 **65** to generate α-alkylidenecyclopentenones in good yield (Table 18).[87]



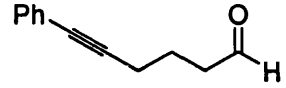
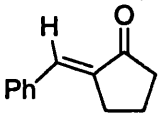
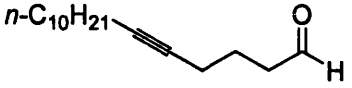
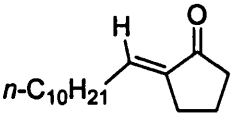
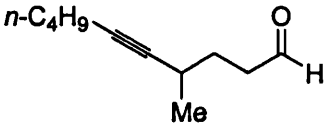
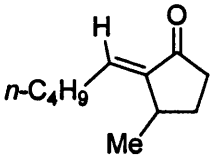
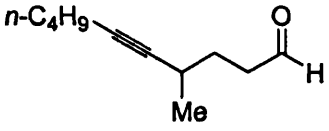
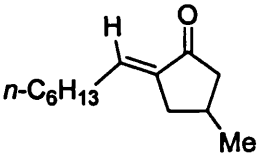
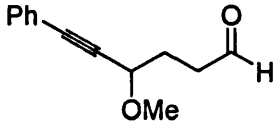
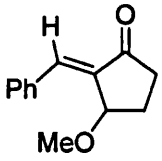
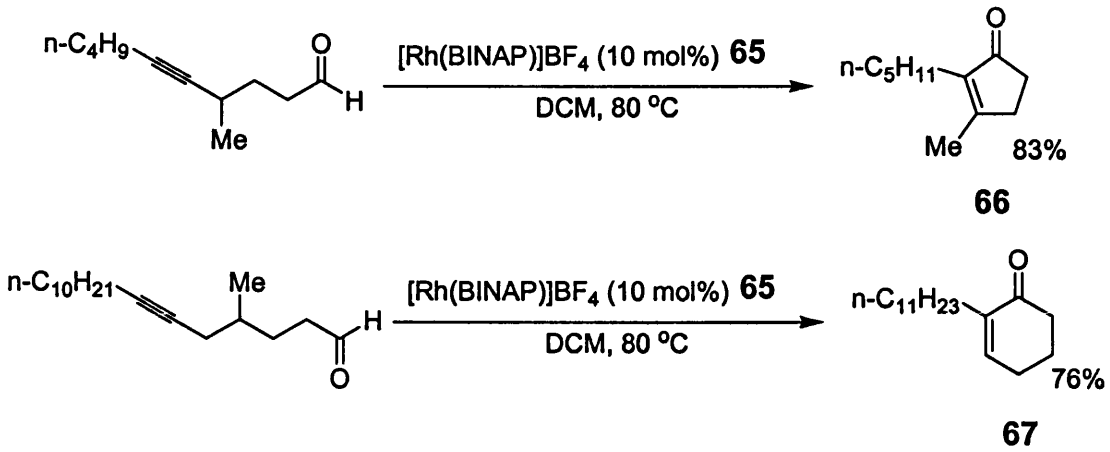
entry	substrate	product	yield (%)
1			78
2			94
3			84
4			82
5			57

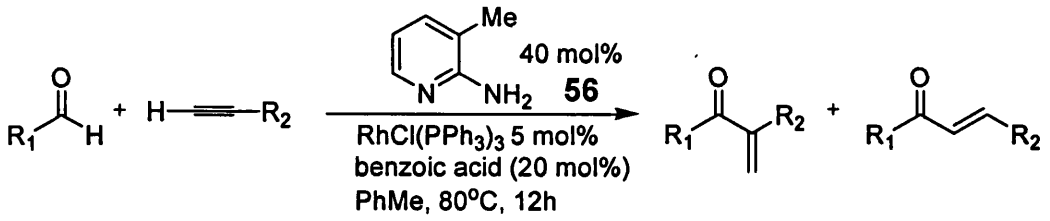
Table 18: Synthesis of alkylidenecyclopentenones

Equally, the same methodology could be effectively applied to 6-alkynal cyclisations.[88] They also reported that at elevated temperature it was possible to get a double bond migration which they proved was rhodium mediated rather than a thermal isomerisation. This reaction delivered cyclopentenones e.g. **66** and cyclohexenones e.g. **67**, in good yield (Scheme 37).[24]



Scheme 37: Double bond migration to cyclopentenones and cyclohexenones

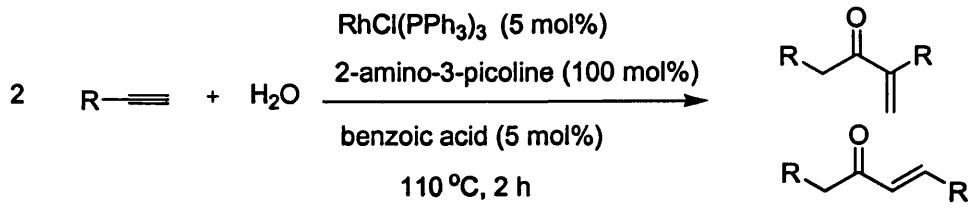
Intermolecular reactions with alkynes are even rarer but there are a few notable examples. The Jun group has investigated hydroacylation with alkynes using their 2-amino-3-picoline **56** system.[89] The group was able to achieve good selectivity for both branched and linear products, varying R-groups on the alkyne and aldehyde.[90] Aromatic aldehydes gave branched products almost exclusively, whilst with aliphatic aldehydes in combination with sterically demanding groups on the alkyne e.g. *tert*-butylacetylene, the linear product was obtained as the major product (Table19).



entry	R_1	R_2	branched: linear	yield (%)
1	Ph	*n*-Bu	100:0	92
2	Ph	*n*-Hex	100:0	93
3	Ph	CH_2Ph	100:0	66
4	4-CF_3-OC_6H_4	*n*-Bu	100:0	95
5	4-MeO-C_6H_4	*n*-Bu	100:0	76
6	naphthyl	*n*-Bu	100:0	83
7	3-thiophenyl	*n*-Bu	100:0	96
8	4-pyridyl	*n*-Bu	100:0	78
9	3-pyridyl	*n*-Bu	100:0	79
10	2-pyridyl	*n*-Bu	-	0
11	*n*-pent	*n*-Bu	78:22	85
12	*n*-pent	*t*-Bu	0:100	74
13	Cy	*n*-Bu	81:19	98
14	Cy	*t*-Bu	0:100	63

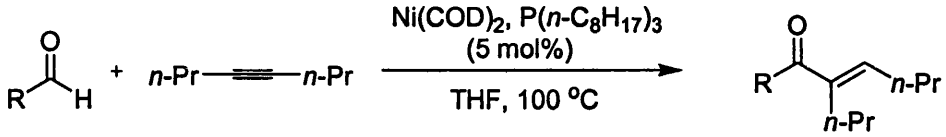
Table 19: Hydroacylation reaction with alkynes using 2-amino picoline

They have also been able to synthesise enones from two equivalents of alkyne and a water molecule (Scheme 38).[91]



Scheme 38: Synthesis of enones from alkyne and water

Nickel has been used as a catalyst for the intermolecular hydroacylation of alkynes. Tsuda has demonstrated that Ni(0) complexes can effect the reaction between aryl and alkyl aldehydes with symmetrical internal alkynes. These systems led to reasonable *E*-selectivity. Unsymmetrical internal alkynes led to a complex mixture of regio-isomers (table 20).[92]

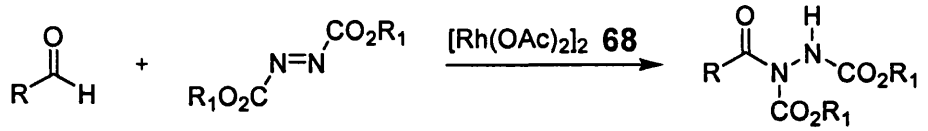


entry	R	Yield (%)	*E:Z* ratio
1	*i*-Pr	93	93:7
2	*n*-Pr	80	95:5
3	Ph	76	79:21

Table 20: Nickel catalysed alkyne hydroacylation

1.7 Hydroacylation reactions with non-C-C unsaturated bonds

Not all examples of hydroacylation are between aldehydes and unsaturated C-C bonds. Lee has shown that hydroacylation is possible across an activated N=N bond. Using a rhodium acetate **68** catalyst at low loadings (1.5-2.0 mol%), at room temperatures a range of aldehydes were reacted to give an efficient synthesis of hydrazine imide functionalities (table 21).[93]



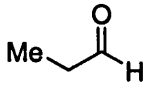
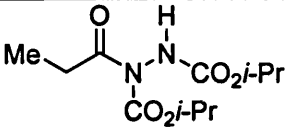
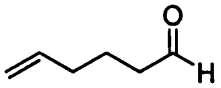
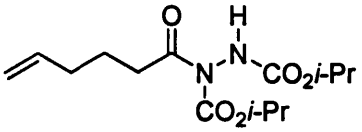
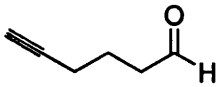
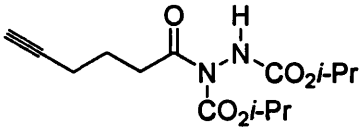
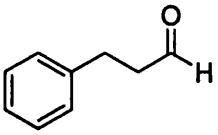
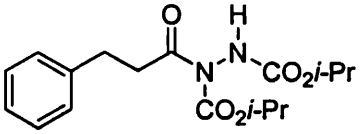
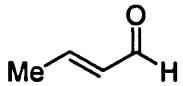
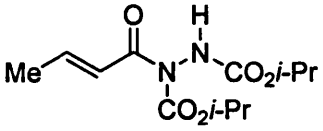
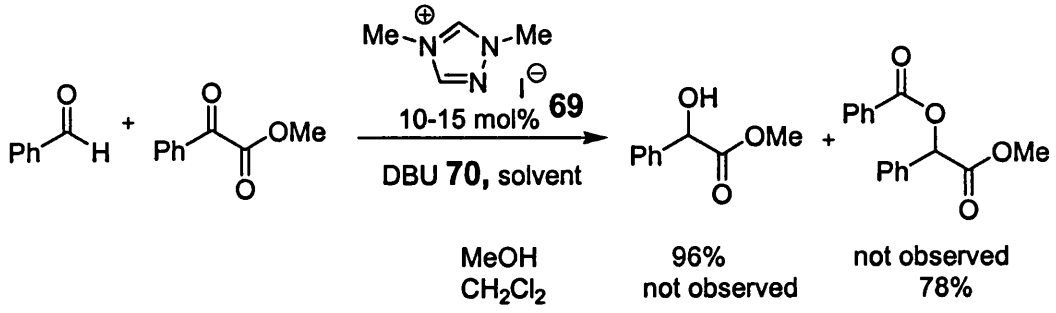
entry	aldehyde	time (h)	product	yield (%)
1		12		97
2		24		77
3		24		74
4		36		81
5		24		84

Table 21: Synthesis of hydrazine imide functionalities

Hydroacylation between an aldehyde and carbonyl group is also possible. Scheidt *et al.* have reported the hydroacylation of a carbonyl with a *N*-heterometeocyclic carbene catalyst **69**.[94] The use of a non-protic solvent such as DCM allowed a hydroacylation reaction to occur using DBU **70** with 10-15 mol% catalyst. Protic solvents such as methanol led to a reduction of the ketone (scheme 39).



Scheme 39: Hydroacylation between an aldehyde and carbonyl group

A range of aromatic aldehydes were used efficiently in the reaction although only non-enolisable aldehydes could be successfully employed. The ketone portion also worked well with substituted aromatic keto-esters (table 22).

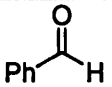
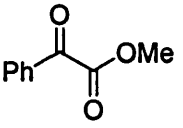
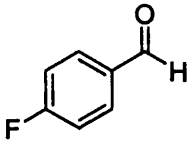
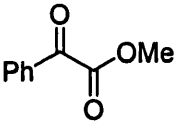
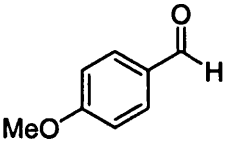
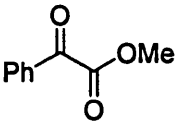
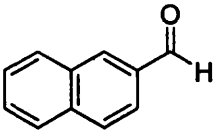
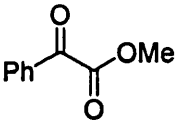
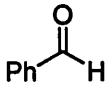
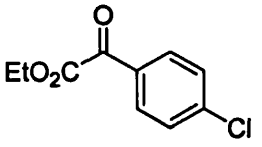
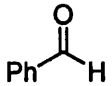
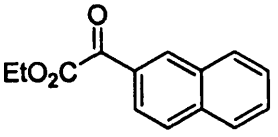
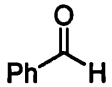
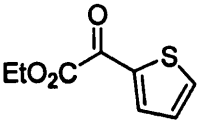
entry	aldehyde	ketone	yield (%)
1			78
2			71
3			77
4			70
5			81
6			78
7			73

Table 22: *N*-meteocyclic carbene catalysed hydroacylation

1.8 Summary

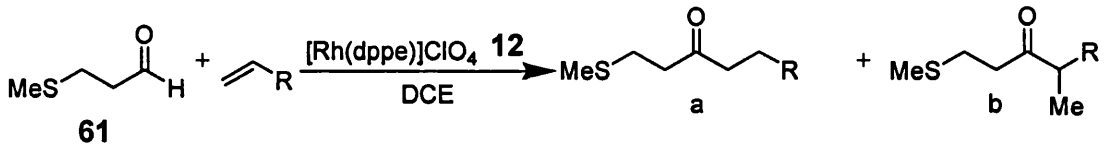
Intramolecular hydroacylation has developed, since early examples, into a synthetically useful process. In particular systems forming five-membered ring systems allow low catalyst loadings with reasonable reaction times. It is possible to carry out diastereoselective and enantioselective reactions with these processes and the reaction has been used in the synthesis of natural products. Larger ring systems have also developed, although not to the same degree due to decarbonylation problems.

Intermolecular hydroacylation is much less developed largely because of issues with competitive decarbonylation. There have been many different approaches to solve this problem, but the most commonly used is a chelation strategy. These systems include using imines as aldehyde equivalents, either directly or formed *in-situ*. However, harsh conditions are often needed for successful reaction. Systems based on salicylaldehyde generally require less harsh conditions but have limited aldehyde substrates. Other methods using sulfur chelation are also presently restricted to a single aldehyde. There is not yet a single set of reaction conditions or catalyst system for taking any aldehyde and reacting it with a range of unsaturated compounds under mild, convenient conditions.

Alkyne hydroacylation is even less developed, however a number of reactions including desymmetrisation and kinetic resolutions have been reported using alkynes.

2 Dithiane substituted aldehydes

As described earlier (chapter one page 37), previous work has identified the use of a β-sulfur atom as a chelating group in intermolecular hydroacylation reactions. This investigation was limited to a single aldehyde although a small range of alkenes had been successfully reacted (table 23).[23]

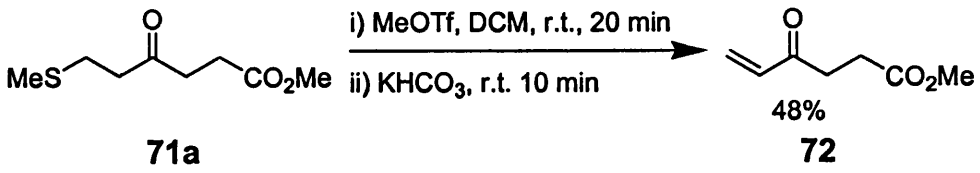


		Products	
Entry	Alkene, R[a]	Yield (%)[b] a	Yield (%) b
1	CO_2Me	60	19
2	$CO_2{}^tBu$	40	6
3	$C(O)NMe_2$	22	0
4	SO_2Ph	0	74

[a] Reactions carried out with 5 mol% catalyst at 70 °C for 2 hours, [b] isolated yields

Table 23: Hydroacylation using β-Sulfide chelating group.

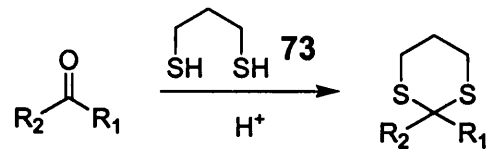
The alkenes were restricted to electron-poor examples, and as can be seen from table 23 both branched and linear products were obtained in some cases. It is possible to remove the –SMe group to allow for further derivitisation of the hydroacylation products however the yield is only moderate.



Scheme 40 Removal of the –SMe group

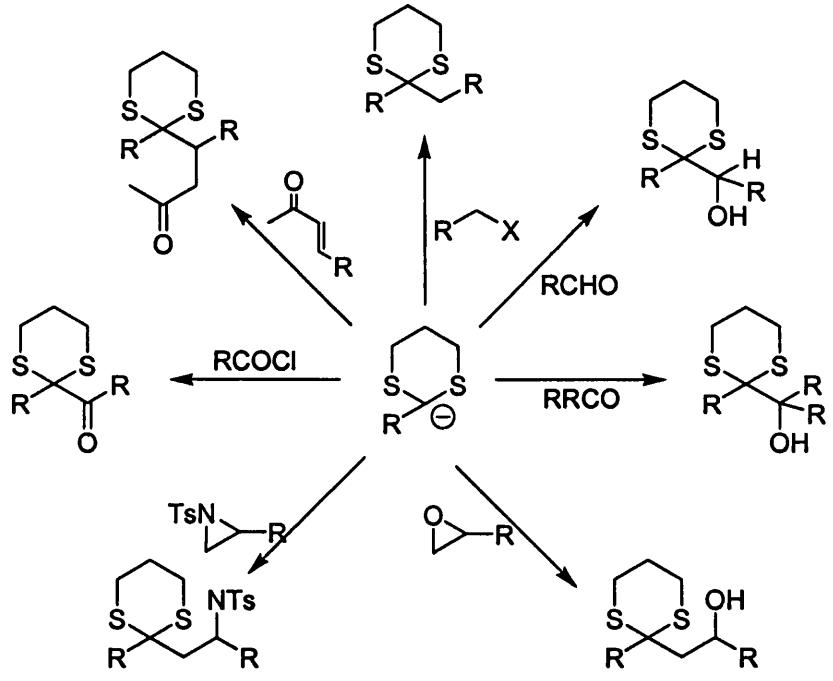
Dithiane groups have received significant interest in recent years due to their importance as carbonyl protecting groups in total synthesis. Synthesised from the

simple condensation of propane-1,3-dithiol **73** with a carbonyl unit (scheme 41), the dithiane group is resistant to both acidic and basic conditions making it a popular protecting group.



Scheme 41: Simple condensation of a dithiane and carbonyl group

As well as their protecting group qualities their umpolung reactivity has led to increased use in modern organic synthesis and as a result several reviews have been published.[95-100] Dithianes have been used in a wide variety of reactions. Perhaps the greatest use is *via* the anion formed from the reaction with strong bases, such as LDA or *n*BuLi, which can react with many functionalities including acylchlorides, aldehydes, alkyl halides and epoxides (scheme 42). [101]



Scheme 42: Possible reactions with dithiane complexes

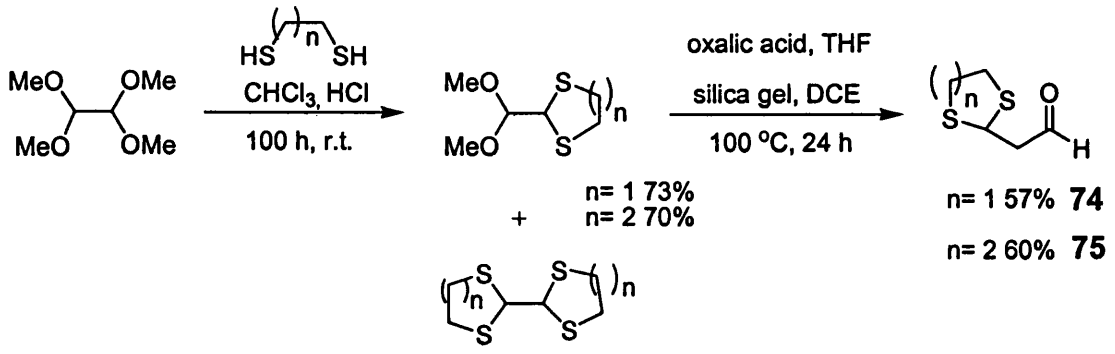
As the use of dithianes has grown, different ways to synthesise them has developed and there are now many variations that can be used. These include reacting alkyl halides with 2-lithio-1,3-dithiane (prepared by deprotonation of 1,3-propane dithiol),

or using 1,3-propanedithiol with tosic acid causing ring opening of dihydropyran.[101, 102]

A particular strength of dithianes as protecting groups, as well as umpolung reactivity, is their stability towards both acidic and basic conditions. However this stability can become an issue as deprotection can be difficult and currently there is no one general method for all substrates. Due to this there are a large number of possible deprotection conditions, the most generic being the use of mercury salts, although toxicity and environmental factors preclude large scale use. Dess-Martin periodane, NBS, selectfluor, $ZnBr_2$ and methyl iodide are other potential methods. [103-108] It is also possible to go directly to the alkane rather than a carbonyl functionality from the dithiane using Raney-nickel.[109]

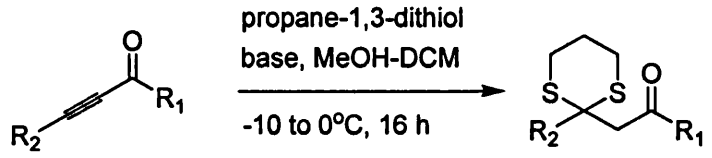
We were keen to establish if a dithiane motif could act as a chelating group in the hydroacylation reaction. If possible this would allow further functionality to be incorporated into any products and allow different removal strategies of the dithiane group giving even more varied final products. It was also hoped that the use of dithianes would prove to be more robust than in the previous work using the β-methyl sulfide aldehyde and so possibly allow both more substituted alkenes or neutral or electron donating alkenes to be utilised in the intermolecular hydroacylation reaction.

Initially it was decided to synthesise an unsubstituted dithiane to see if any reactivity could be observed. This was achieved in two ways. The first synthesis attempted was successful but needed extremely long reaction times in particular for the first step. This part of the sequence also involved the production of an unwanted side product which made the purification of the desired product more difficult. The yields for this reaction were also moderate, in particular with the second step, and it would be unlikely that this synthetic method could be extended to the production of substituted dithiane products. Despite these problems both the dithiane **74** and dithiolane **75** aldehydes were successfully synthesised (scheme 43).



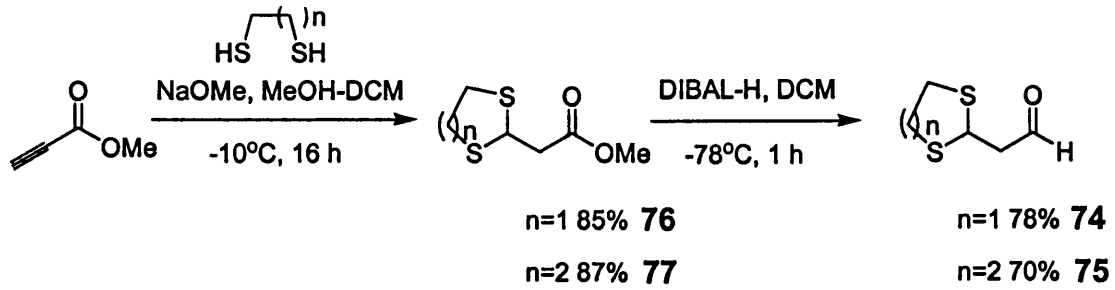
Scheme 43: Initial synthesis of unsubstituted dithiane and dithiolane aldehydes[110]

The second approach was much more successful. In addition to the methods mentioned earlier (scheme 41 and 42) Ley has designed a synthesis of dithianes from alkynes which is applicable to many substituted alkyne molecules (scheme 43).[101]



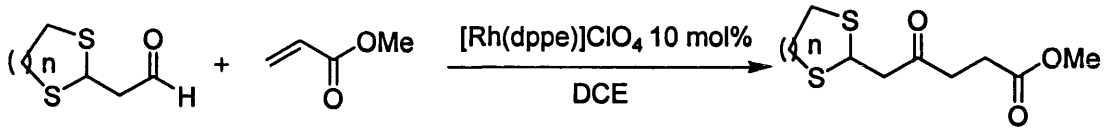
Scheme 44: Synthesis of dithianes by Ley

This is designed for the production of both substituted and unsubstituted aldehydes. However it is reported that unsubstituted ynals do not work as successfully, therefore in these cases an ester starting material must be used which can then be easily reduced to the aldehyde using DIBAL-H. This methodology allowed the reaction to be completed within a 24 h time period and with an overall increase in yield (scheme 45).



Scheme 45: Second synthesis of unsubstituted dithiane aldehyde

Initially both a 6-membered dithiane and 5-membered dithiolane were synthesised to see if there were any differences in reactivity. The most successful reaction with the previous aldehyde had been carried out with methyl acrylate. It was therefore decided to use this as a test system for the hydroacylation reaction. Pleasingly both reactions were successful (table 24 entries 2 and 4).



entry[a]	starting material (n)	aldehyde (yield %)	temperature (°C)	reaction time (h)	product	yield of product (%)[b]
1	1 **74**	78	60	16	**78**	73
2	1 **74**	78	70	4	**78**	75
3	2 **75**	70	60	4	**79**	78
4	2 **75**	70	70	1.5	**79**	82

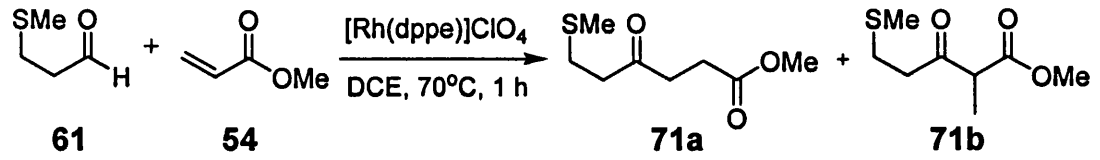
[a] Reactions carried out with 10 mol% catalyst, [b] isolated yields

Table 24: Effect of temperature and dithiane or dithiolane group on hydroacylation reaction

There were significant differences between the substrates; the dithiolane took much longer to go to completion (4 hours compared to 1.5 hours). With both aldehydes the sulfur is obviously still able to coordinate to the rhodium, as the reaction does take place, and so presumably little decarbonylation is occurring. Exactly why there is a reactivity difference has not been completely determined. Some possible arguments include; the electronics of the 5-membered ring perhaps do not allow bonding interactions as strong as those in the dithiane. Or in reverse, it is possible too strong a bond is being formed with the dithiolane. It is feasible that the dithiolane reaction (and to a lesser extent that of the dithiane) was slowed down by a *bis*-chelation so no free site on the rhodium remained for reaction as neither reaction was as fast as the β-methylsulfide aldehyde originally investigated. Despite the increase in reaction time the yields for both reactions were equivalent. Both gave high enough yields to indicate decarbonylation was not the predominant reaction pathway.

It was also apparent that the reaction temperature had an effect in increasing the reaction rate. This is not surprising as similar observations were found with the original aldehyde. Again, despite longer reaction times at lower temperatures almost identical yields were reported. This indicates that decarbonylation is not a major problem within the reaction even at the lower temperature.

It also seems that the dithianes do react in a different fashion to the single sulfur linkage, in that only linear products were obtained. The original aldehyde **61** gave a mixture of branched **71b** and linear **71a** products with methyl acrylate **54** (scheme 46).

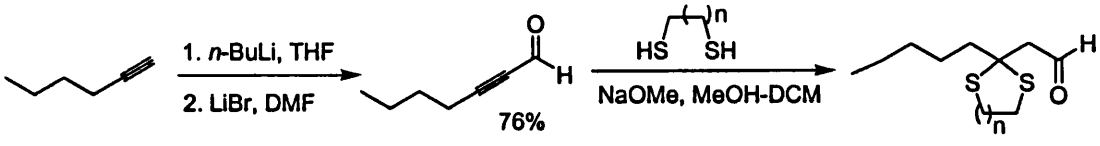


61 **54** **71a** **71b**

Scheme 46: Reaction of β-methylsulfide aldehyde with methyl acrylate

The fact only linear products are formed with the dithiane substrate may be due to the ability of both sulfurs to bind or "replace" each other if the chelate is lost. It may also be due to the greater steric bulk around the catalyst centre effectively blocking the formation of the branched product. This greater selectivity is an advantage as it allows for a very clean reaction and avoids any complex purification issues.

Given these initial positive results it was decided to try adding a substituent onto the dithiane. The first of these was simply an alkyl chain and again both the dithiane **82** and dithiolane **81** were made using the methodology developed by Ley (scheme 47).[101]



80

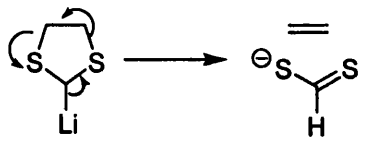
n= 1 76% **81**

n= 2 78% **82**

Scheme 47: Formation of alkyl substituted dithiane aldehydes

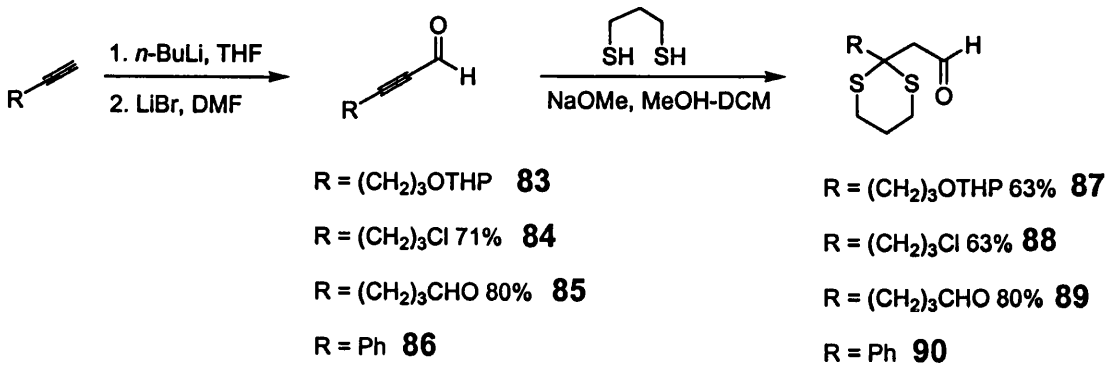
The results from the hydroacylation reaction with these aldehydes were mixed. The difference between the 6- and 5-membered rings became much more pronounced (Table 25). While the 6-membered dithiane aldehyde underwent hydroacylation to completion after reaction for 16 hours the ditholane did not produce any obvious product even after reaction for 72 hours. This indicated that either the dithiolane could not achieve coordination for long enough to promote the hydroacylation reaction when any other steric influences are involved, further reinforcing the possible problems mentioned earlier. Or possibly it underwent binding that was too strong to allow reaction, through for example *bis*-coordination. Even when the catalyst loading was increased to 20 mol% no reaction was observed. It is possible the more strained conformation of the 5 membered ring, with substitution, does not allow the lone pairs on the sulfur to be orientated in the correct alignment for coordination to the rhodium. The time taken for the reaction of the 6-membered dithiane was significantly longer than the unsubstituted dithiane but again only the linear product was observed. This result illustrates that it is possible to add additional substitution to the reaction thus extending the range of substrates. As was hoped no further increase in temperature was needed to help this reaction go to completion and a good yield (77%) was obtained.

From this point it was decided to concentrate on the dithianes. These are much more commonly used in synthesis as dithiolanes cannot be used to form an anion, as although it will deprotonate easily it then decomposes by a similar mechanism as lithiated THF (scheme 48).[111]



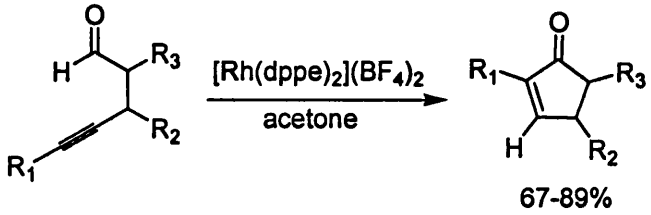
Scheme 48: Decomposition of dithiolane anion

A range of aldehydes were subsequently synthesised (scheme 49) and hydroacylation reactions attempted to investigate the range of substitution and functionality possible within the aldehyde.



Scheme 49: Synthesis of substituted dithiane aldehydes

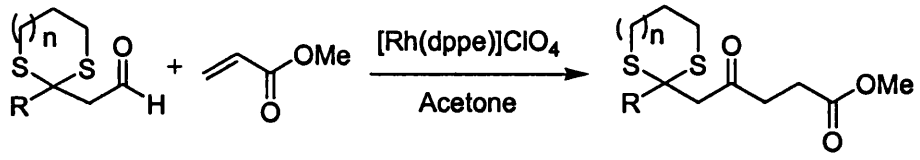
A limited solvent screen performed with the hydroacylation reaction previously had identified DCE as a good solvent for the reaction. However Fu carried out a solvent screen when investigating intramolecular *trans*-hydroacylation of alkyne and identified acetone as the best solvent with a similar catalyst to that we employ (scheme 50).[24, 25]

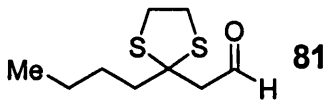
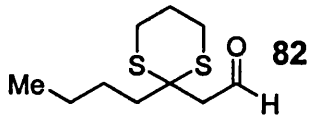
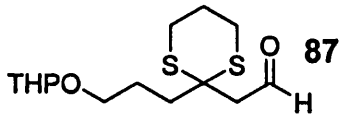
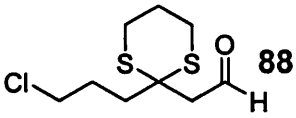
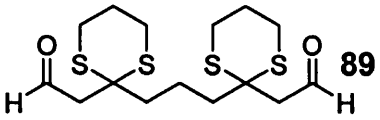
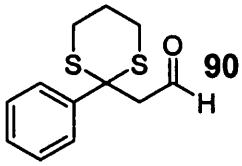


Scheme 50: Intramolecular hydroacylation using acetone as solvent

It was decided to see if the use of acetone as reaction solvent led to any improvements within our system. It was found the reaction temperature could be lowered to 55 °C with no loss of yield or extension of reaction time and the results were more reproducible. This is presumably because the catalyst is more stabilised by acetone than DCE. This would slow down any decomposition of the catalyst increasing the lifetime of the active catalyst. Another advantage is that the catalyst activation step in the reaction is much more controlled in acetone with the colour change being significantly more pronounced (a light orange to dark yellow in DCE to a dark orange to light yellow in acetone). The number of equivalents of alkene originally used in the reaction (5 equivalents) was also high and it was uncertain whether this level was required for speed of reaction. The alkene equivalents were reduced to two and there was no increase in reaction time or decrease in yield using both acetone and DCE. A single equivalent was also tried and was successful in

roughly the same time frame. Subsequent reactions were therefore carried out using two equivalents only and acetone as solvent, to ensure complete reaction.



entry[a]	aldehyde	reaction time (h)	product	yield of product (%)[b,c]
1	 **81**	72		No reaction
2	 **82**	16	**91**	77
3	 **87**	18	**92**	70
4	 **88**	18	**93**	72
5	 **89**	8	**94**	84
6	 **90**	72		No reaction

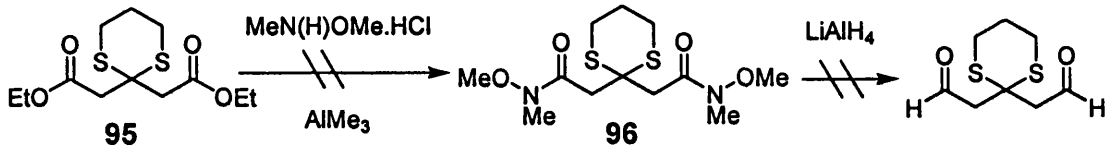
[a] Reactions carried out with 10 mol% catalyst at 55 °C, [b] isolated yields, [c] only linear isomers observed

Table 25: Aldehyde assay in the hydroacylation reaction

As can be seen from table 25 several aldehydes were synthesised however the results of the hydroacylation reaction were mixed.[112] The THP protected alcohol **87** underwent reaction going to completion in eighteen hours in good yield. The chloroaldehyde **88** also worked well in an overnight reaction. It is worth noting that while the product of this reaction is relatively stable, the aldehyde itself is extremely unstable and had to be used as soon as it was synthesised in order to get a good yield for the reaction. Both these reactions indicate the system has good functional group

tolerance. The THP reaction also shows an acceptance of reasonably large and coordinating functional groups when placed slightly away from the reactive centre. Once again only the straight chain products were obtained with no trace of the branched isomer.

The *bis*-aldehyde **89** undergoes hydroacylation easily. This compound gives solely the double hydroacylated straight chain product. Close monitoring of the reaction by TLC only indicated a single product throughout. It is possible that one end of the complex undergoing hydroacylation helps promote reaction at the other end. It is feasible to suggest, in this vein, that the catalyst finds it much easier to react in a *pseudo*-intramolecular way moving from one end of the molecule to the other than finding a completely new aldehyde to react with. This reaction is very clean and does not appear to give any other products, which may help to support this theory. It is also interesting that the time needed to go to completion is significantly less (eight hours for the *bis*-aldehyde compared to eighteen hours for the alkyl substituted monoaldehyde) than that with the alkyl substituted aldehyde even though a similar chain length is involved. As the reaction time for this substrate is in fact significantly lower than for any of the other substituted aldehydes it reinforces the advantage the double reaction must bestow. It was hoped to synthesise a *bis*-aldehyde directly linked to the dithiane to see if it was indeed an advantage to have two aldehyde functionalities or if the increase in reaction rate was also due to having two dithiane functionalities. Unfortunately although a dithiane with a double ester group **95** was easy to synthesise, the DIBAL-H reaction to create the two aldehydes was difficult. A second attempt to create the aldehyde was performed by trying to form the Weinreb amide **96** which would have allowed the use of $LiAlH_4$ and Red-Al as well as DIBAL-H to affect the transformation to the aldehyde (Scheme 51).



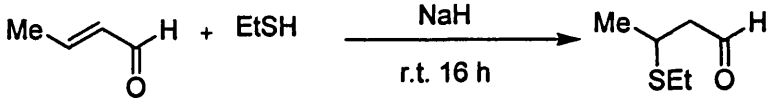
Scheme 51: Conversion of the ester to weinreb amide to aid conversion to the aldehyde

Unfortunately this was also unsuccessful despite repeated attempts so further investigation of this result was not possible at this time. Reports in the literature

support the case for abandoning work on this aldehyde as it is not uncommon for aldehydes close to very bulky groups [113] to be extremely hard to form.

Where the R-group on the aldehyde is a phenyl substituent (table 25 entry 6) no reaction was observed to take place. This result was presumably because the phenyl group was too sterically hindered to allow the reaction to take place with the already present large dithiane. In this aldehyde the phenyl group is very close to the centre where the reaction actually takes place and therefore may inhibit the dithiane from coordinating to the rhodium. It is possible that moving the phenyl group further away from the reactive centre may have allowed this functional group to be on the starting material. Unfortunately this theory could not be tested because of the unavailability of starting materials. It is also possible the rhodium centre underwent л-coordination to form a η^6-complex with the phenyl group stopping the reaction. It is more likely that a steric effect was observed however, as the only other aldehyde synthesised that did not undergo hydroacylation was the *iso*propyl substituted example. This aldehyde would be highly unlikely to coordinate to the rhodium directly but is a bulky group and so a steric problem would be much more plausible. Work with other substrates also involving the use of phenyl containing functionalities showed no problems of reaction inhibition which again argues against this being the problem.

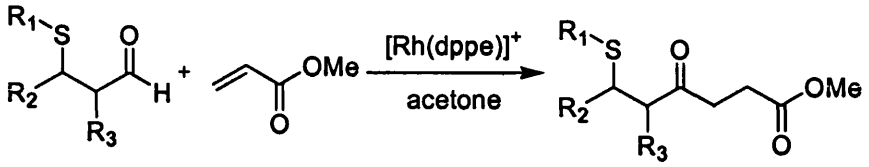
The Willis group developed a range of β-substituted sulfide-aldehydes for use within a reductive-aldol reaction.[114] These aldehydes were easily prepared from the corresponding enals in a neat reaction with ethyl or phenyl-thiol and sodium hydride (or triethylamine) (for example scheme 52). The addition of the sodium hydride needed to occur very slowly to avoid the production of a polymer caused by the extremely exothermic reaction on addition of the sodium hydride.[115] This was less of a problem when using triethylamine but a slow addition was still required. The resulting products were purified by short path distillation and then required storage at low temperatures (-5 to -20°C) at which they remained stable for several months.

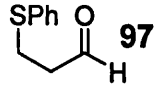
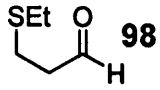
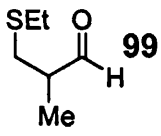
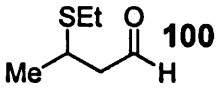
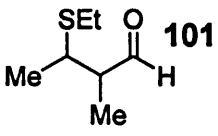
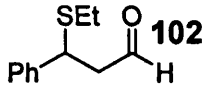


102

Scheme 52: Synthesis of substituted sulfides

These same aldehydes have been employed in the hydroacylation reaction with good results. The additional substitution of these aldehydes, compared to the original aldehyde that was used, allowed further investigation into the tolerance of the reaction (Table 26).[116]



entry[a]	*starting material*	*time (h)*	*product*	*yield (%)*[b]	*product ratio linear:branched*
1	 **97**	5	**103**	92[c]	>20:1
2	 **98**	1	**104**	80	6:1
3	 **99**	16	**105**	83	>20:1
4	 **100**	16	**106**	77	>20:1
5	 **101**	20	**107**	76[c]	>20:1
6	 **102**	16	**109**	87	>20:1

[a] Reactions carried out with 10 mol% catalyst at 55 °C, [b] isolated yields [c]reactions carried out by RL Woodward

Table 26: Substituted sulfides in the hydroacylation reaction

These results are a further indication that the reaction is able to tolerate extra steric hindrance. In common with the substituted dithianes the results show that adding extra substituents to the aldehyde results in increased reaction times, of eighteen hours were required for complete conversion. These results seem to indicate that the steric bulk around the active catalytic centre is important in helping understand the reaction rate. It is envisaged that the increased sterics decelerate the hydrorhodination step of the catalytic cycle. If this is (or becomes) the rate determining step of the whole cycle it would be easy to see why there is such a large increase in time needed

for the reaction to go to completion even with the addition of a single Me -group. (Table 26)

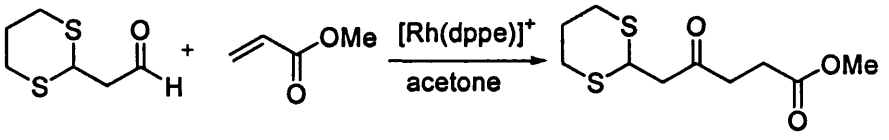
The two reactions with different sulfides- **97** and **98** give a comparison to the reaction time of the original methyl-sulfide aldehyde. The ethyl sulfide **97** has virtually the same reaction time (1 hour) while the phenyl sulfide **98** takes longer to go to completion (five hours). This indicates there is an effect on the speed of reaction from the substrate attached to the sulfur. This may be due to the extra steric bulk around the sulfur as sterics do seem to play an important role in the reactivity of the system. It is also possible that the electronics of the sulfur may be the controlling factor in the speed of these reactions. The phenyl sulfide **97** would probably have less ability to donate its electrons to the rhodium during the reaction and this may slow the system down. It may also be a combination of these factors that help to govern the reactivity, interestingly there was less observed branched products from these aldehydes than in the methysulfide aldehyde **61** reaction. It was not at all unexpected for only straight chain products to be obtained from the aldehydes with substitution in the β-position in an argument similar to that of the extra steric bulk precluding the formation of the branched product with the dithianes. However, the reduction in the branched to linear ratio obtained from the ethyl sulfide aldehyde **98** (1:4 with methyl sulfide to 1:6 with ethyl sulfide) was less expected. In addition, the phenyl sulfide was further reduced to a 1:10 ratio of branched: linear. This may indicate that the electronics of the aldehyde influence the stereocontrol of the reaction. The other possibility is that the differences in sterics on the sulfide group control the stereoselectivity of the reaction. The determination of which of these reasons was the most important in governing the stereocontrol would be an important area to investigate in the future.

The results with both the phenylsulfide **97** and the β-phenyl substituted aldehyde **102** are among the more interesting. With compound **102** the phenyl group is in the equivalent position as on the dithianes but unlike the dithiane it was fully successful. This shows that the phenyl group is unlikely to be coordinating to, and consequently blocking the catalyst. The fact that this substrate works well, in an overnight reaction, indicates that any steric problems must be a combination of the phenyl group and dithiane rather than purely due to the phenyl group alone. The aldehyde with substitutions on both the α- and β-positions **101** was the slowest of all these aldehydes to react taking twenty hours compared to sixteen for all the other substituted

examples. This again is an indication of the effect of increased reaction times with increased substitution near the reactive centre. In the dithiane examples the dithiane group itself is very bulky, when this is combined with the large phenyl or *iso*-propyl group it is understandable that the sterics involved could limit the reaction.

Unfortunately the dithianes also give a slower reaction time than with 3-methylthio propionaldehyde **61**. This may be because the additional steric bulk around the active centre may reduce the efficacy of the reaction or it is possible that the ability of the two sulfurs to bind may 'tie-up' the catalyst and so reduce the rate of reaction. As already stated (chapter 1 page 8) Bosnich noted that the speed of the reaction was decreased in more concentrated reaction mixtures due to the substrates binding to the catalyst preventing it from moving on to the next stage in the catalytic cycle.[20] As two sulfurs are present in the dithianes it is possible they have an equivalent ability and block the catalyst to a higher degree than 3-methylthio propionaldehyde **61**.

For all these reactions the catalyst loading was relatively high- 10 mol% this is double the loadings used in the original reaction. This loading was chosen to allow a convenient reaction times. However it has been shown that much lower catalyst loadings can be used although this leads to greatly extended reaction times (Table 27).



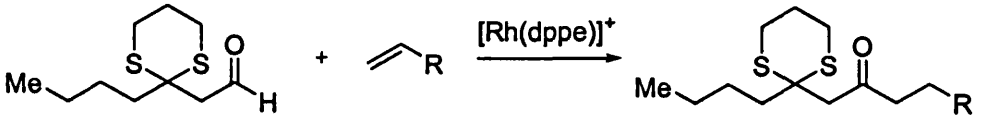
entry[a]	*catalyst loading (%)*	*reaction time (h)*	*yield (%)*[b]
1	10	4	77
2	2.5	24	78
3	1	48	70

[a] Reactions carried out at 55 °C, [b]isolated yields

Table 27: Catalyst loading trials

For these trials the most reactive systems were chosen in order to give the best chance for lower loadings to be successful and to make it easier to follow the timings of the reactions. As can be seen the loading can be reduced to much more reasonable levels with no appreciable loss in yield.

As well as showing the reaction could tolerate a range of aldehydes it was also important to investigate the range of alkenes that could be used. The chosen dithiane aldehyde for these reactions was one of the slower reacting substrates to ensure that the reactivity was applicable to all substrates. Unfortunately the dithianes did not allow a greater range of alkenes to be used than had previously been discovered. As the reaction times of the dithianes are longer than the original aldehyde this is not unexpected. The hoped for extra stability of the dithiane- rhodium complexes may have an inverse effect in that they are more coordinating but as such 'tie-up' the catalyst for longer and stop the reaction turning over as quickly. The much larger steric bulk around the catalyst may also be a contributing factor in slowing the reactions. This is likely given the results from the other aldehydes. The reaction is therefore limited to mono-substituted highly electron withdrawing alkenes.

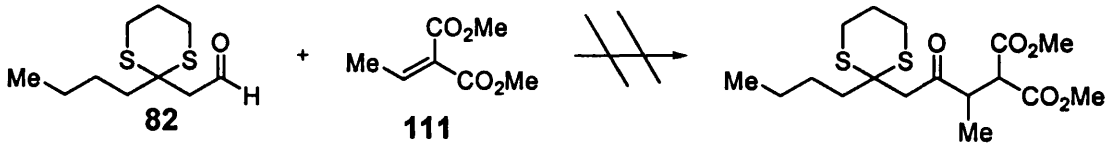


entry[a]	*R*	*time (h)*	*product*	*yield (%)*[b]
1	CO_2Me	16	**91**	77
2	$CO_2{}^tBu$	16	**109**	70
3	$CONMe_2$	16	**110**	68
4	$P(OEt)_2$	48		0
5	$(CH_2)_5CH_3$	48		0

[a] Reactions carried out with 10 mol% catalyst at 55 °C, [b] isolated yields

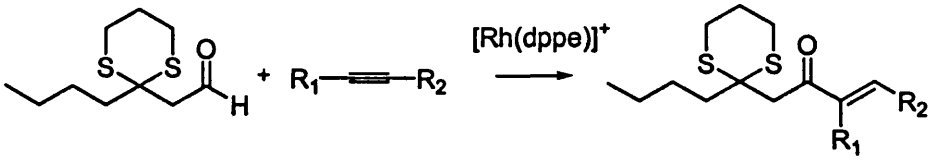
Table 28: Hydroacylation reaction of dithiane aldehydes with alkenes

Although a number of other alkenes including vinyl phosphonate, allyl acrylate and cyanostyrene were also tried in the reaction no discernable products were isolated. These results do limit the applications of this reaction. Although not expected to work given the above results dimethyl ethylidenemalonate **111** was also tried in the reaction. As predicted this did not prove to be reactive enough to give any discernable products.



Scheme 53: Reaction with dimethyl ethylidenemalonate 111

While the work with alkenes was disappointing, it was discovered that alkynes are significantly more reactive allowing short reaction times, a reduction of catalyst loadings and a much wider range of substrates (Table 29). Mono-substituted alkynes do not seem to be affected by electronic effects in that they can have electron withdrawing, donating or neutral groups on them and still react in similar reaction times and yields. In addition to this di-substituted alkynes were also successful which is in complete contrast to the alkenes where only mono-substituted examples were successful.



entry[a]	R_1	R_2	*time (h)*	*product*	*yield (%)*[b]
1	H	$(CH_2)_3CH_3$	16	**112**	75
2	H	$(CH_2)_4Cl$	16	**113**	73
3	H	CO_2Me	16	**114**	75[c]
4	CO_2Me	CO_2Me	18	**115**	71[d]
5	CH_2OH	CH_2OH	18	**117**	83

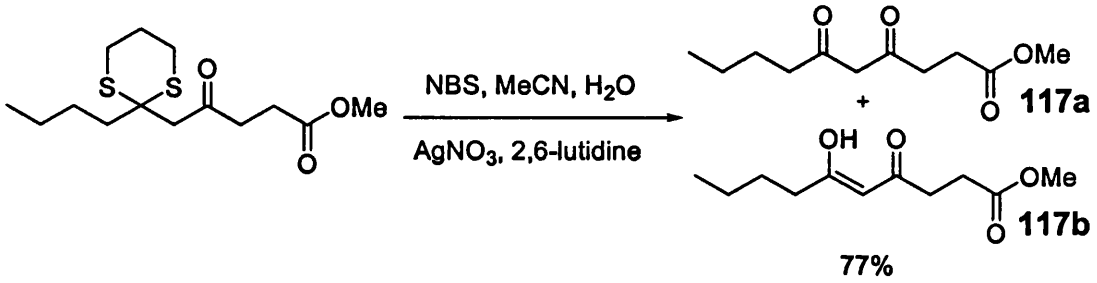
[a] Reactions carried out with 5 mol% catalyst at 55 °C, [b] isolated yields, [c]ratio of *E:Z* 5:1, [d] ratio of *E:Z* 3:1,

Table 29: Hydroacylation reaction of dithianes with alkynes

The reactivity of alkynes was such that the catalyst loadings could routinely be reduced to 5 mol% without extending the reaction time. As can be seen from table 29 the alkynes showed reactivity better than the best alkene (methyl acrylate takes 18 hours to go to completion with 10 mol% catalyst giving 77% yield). The stereocontrol of these reactions was also remarkable with only a single product being formed in the majority of cases despite a possible three outcomes of branched, linear -

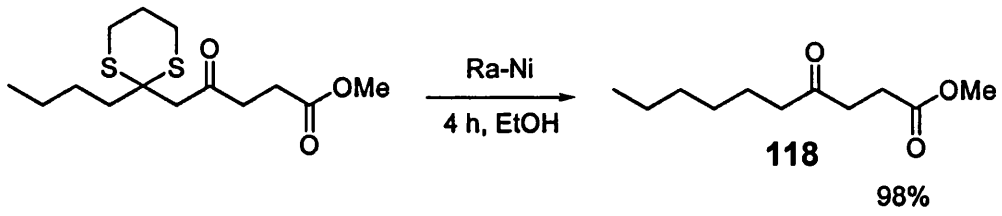
Z and linear *E*. The extent of this control was investigated in more depth, described later.

It was also important to prove that the products from these reactions were able to undergo deprotection to both the carbonyl group and alkane. This emphasises the extra advantages that dithianes generate compared to the simple sulfur-methyl linkage. It was also important with the deprotection to the carbonyl to avoid the use of mercury salts to indicate that the reaction could in the future be scaled up without such major environmental or safety concerns. The reactant that proved to be the most successful for this reaction proved to be NBS in combination with silver nitrate and 1,6-lutidine (Scheme 54).[117, 118]



Scheme 54: Deprotection of dithiane group to ketone

These conditions gave the product **117** in 77% yield with only a 30 minute reaction time. The major product obtained from the reaction is actually the enol form of the product presumable due to the stabilisation effects of the other ester group within the molecule. The other deprotection back to the alkane was even more straight forward. Raney-Nickel was able to take out the dithiane in almost quantitative yields with only a 4 hour reaction time (scheme 55).[109, 119]

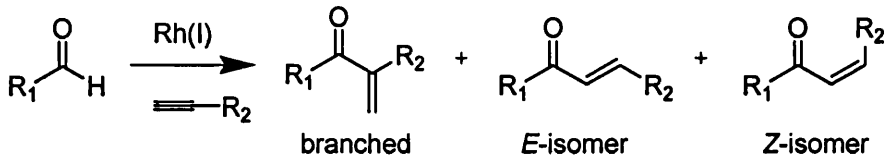


Scheme 55: Ra-Ni deprotection of dithiane

Both these reactions give good yields and would therefore represent useful strategies for further manipulation of the hydroacylation products as required. These results prove that the dithiane group is suitable as a chelate in the intermolecular hydroacylation reaction. The dithiane group allows for significant variation of starting materials of both the aldehyde and alkene/alkyne. It can give a wide variety of products both initially and after conversion of the dithiane group to other functionalities.

2.1 Alkyne investigation

One of the most interesting discoveries during the dithiane investigation was the reactivity of alkynes. The fact that every alkyne tested not only reacted but did so quickly and most with a good level of stereocontrol, is highly unusual and very encouraging. As has been mentioned earlier, three different isomers are possible from alkyne reactions; this makes it even more interesting in that it appears this reaction has almost complete regio- and stereochemical control.

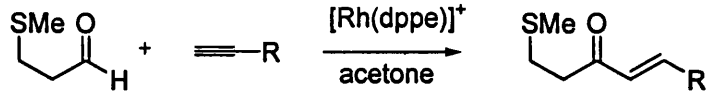


Scheme 56: Possible products from hydroacylation with alkynes

Hydroacylation with alkynes is even less common than alkenes, as mentioned in the introduction. Some work has been done with alkynes recently for example intramolecular systems, kinetic resolutions and parallel kinetic resolutions have been investigated by the Fu group (chapter 1, page 40).[24, 25] The Tanaka group have also worked in intramolecular systems with alkynes developing route to both substituted five and six membered ring systems with good sterocontrol.[87, 88] They were also able to promote double bond migration to give, for example, α,β-disubstituted cyclopentanones (chapter 1, page 44). Additionally Jun has worked with alkynes in intermolecular systems and was able to achieve good stereocontrol of both the branched and *E*- linear isomer by the choice of aldehyde and alkyne (chapter 1, page 45).[89, 90]

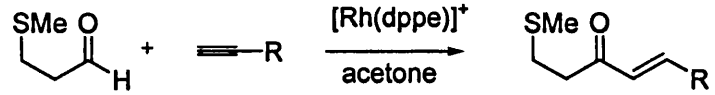
We wanted to discover the full tolerance of the reaction to functional groups on the alkyne and identify the mildest conditions possible. It was also important to see if the stereocontrol would continue for all substrates. In particular the internal alkynes had been little explored in their functional group tolerance and selectivity in cases where two different groups were attached to the alkyne. In order to facilitate this 3-methylthio propionaldehyde was used as it is still the fastest reacting aldehyde, based on the results with methyl acrylate, and is commercially available. It was also

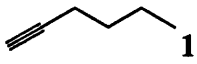
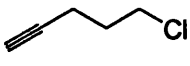
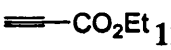
necessary to ensure that the alkynes were as reactive with the sulfide linkage as with the dithianes.



Scheme 57: Hydroacylation reaction of 3-methylthio propionaldehyde and alkynes

The results obtained from these reactions were very good.[116] The first series of investigations were performed using the same conditions as previously identified- 55 °C, 5 mol% catalyst, two equivalents of alkyne and acetone as a solvent. The same series of mono-substituted alkynes used in the dithiane reactions were tested and all went to completion within 1 hour giving yields of 80% and above. This reactivity is comparable to the previously best substrate- methyl acrylate. Once again single isomers were obtained from the reactions with the *E*-linear forms isolated for all but the dimethyl acetylenedicarboxylate. As can be seen from table 30, in the case of 1-hexyne **121** almost quantitative yields were obtained. The chloro-substituted alkyne **122** gave similarly high yields and both these reactions gave excellent stereocontrol.



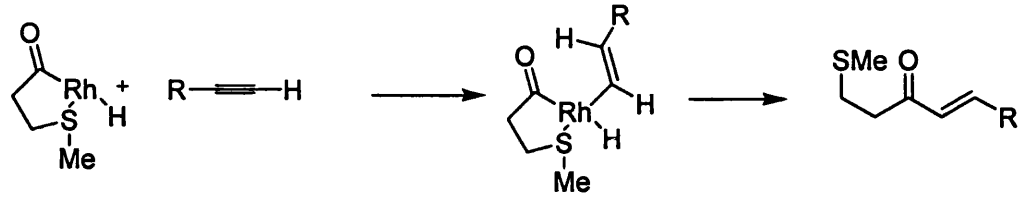
entry[a]	*alkyne*	*product*	*yield (%)*[b]	*ratio of products* E:Z
1	 **119**	**122**	98	>20:1
2	 **120**	**123**	85	>20:1
3	 **121**	**124**	69	1:2

[a] Reactions carried out with 5 mol% catalyst at 55°C for 1 hour, [b] isolated yields

Table 30: Initial investigation into alkyne reactivity

As can be seen in both the dithiane and sulfide case where an ester group is directly attached to the alkyne (in both the mono- and di-substituted example) the selectivity of the reaction markedly decreases (entry 3, Table 30 and entry 3 and 4, Table 29). With the other alkynes only one isomer is observable and it is possible to attribute this to a syn elimination in the mechanistic pathway. As shown in scheme 57 it is

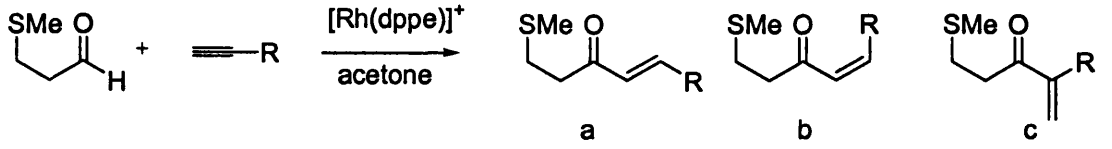
feasible there is a stereoselective addition to the alkyne giving the *E* alkene with respect to the Rh and R group. This in turn retains its stereochemistry during a *syn* elimination leading to the products observed.

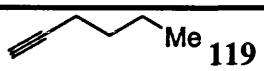
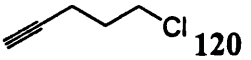
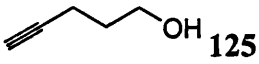
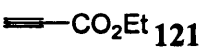
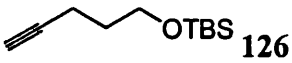
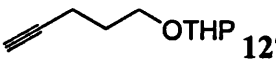
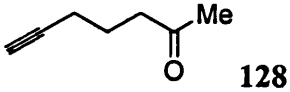
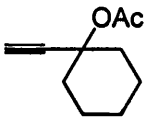
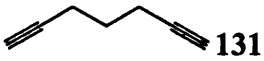
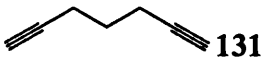
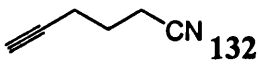


Scheme 58: *Syn*-elimination pathway

In the case of the ester-alkyne this cannot be solely the case. When the products of the reaction were re-exposed to the reaction conditions no change in the ratios of products was observed indicating that the product does not racemise. This perhaps shows that it is unlikely that the reaction does proceed along a syn-elimination pathway and subsequently racemises to the ratios observed at the end of the reaction. This in turn indicates that another mechanistic pathway must be in operation in these cases.

The range of functional groups that could be tolerated by the reaction was then investigated.



entry[a]	*alkyne*	*product*	*yield of isomer*[b]		
			a	b	c
1[c]	 119	122	98	0	0
2[c]	 120	123	85	0	0
3[c]	 125	133	95	0	0
4[c]	 121	124	23	46	0
5[c]	 126	134	87	0	0
6[c]	 127	135		0	0
7[c]	 128	136	69	0	0
8[c]	 129	137	89	0	0
9[c]	 130	138	79	0	0
10[d]	 131	139	74	0	0
	Single reaction				
11[c]	 131	140	60	0	0
	Reaction at both ends				
12[c]	 132	141a	0	0	68

[a] Reactions carried out with 5 mol% catalyst at 55 °C for 1 hour, [b] isolated yields, [c] 2 equivalents of alkyne used, [d] 0.5 equivalents of alkyne used

Table 31: Scope of alkyne component in hydroacylation reactions

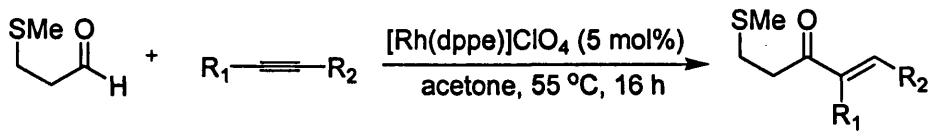
It is worth noting all the alkynes attempted were highly successful and it seems likely that many other functional groups would be equally reactive in the conditions employed for the above reactions but time and resources prevented an even more extensive search. As can be seen from table 31 a large range of functional groups were tolerated. As well as alkyl groups chlorine atoms **120**, ketones **128** and ester **121**

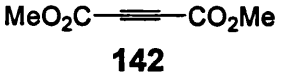
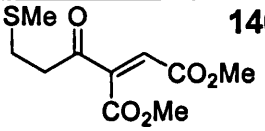
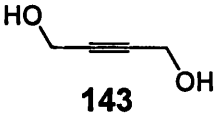
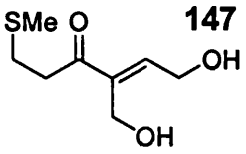
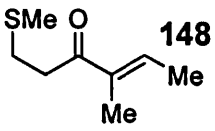
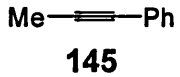
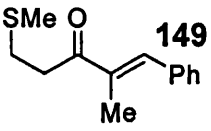
groups were all successfully reacted. Even more interestingly free alcohols **125** gave very good yields and protecting them with both a silicon protecting group **126** and THP **127** also gave very high yielding reactions. The tolerance of free alcohol groups indicates that the catalyst is not affected in a detrimental way by the presence of alcohol groups. An acetate containing alkyne also gave good yields. In this case the groups attached to the alkyne were fairly bulky but this did not seem to affect reactivity or yield in any way.

The dialkyne had particularly good reactivity in that it was possible to induce reaction of the dialkyne at one end **139** or at both ends **140** of the molecule depending on the number of equivalents of the alkyne that were used. With two equivalents of the alkyne the mono-reacted product was the only isolatable result in good yield (74%). However, when 0.5 equivalents (compared to the aldehyde) of the alkyne was used the *bis*-reacted product was obtained (60%) with a small amount of the mono-reacted product (5%). In both cases the same reaction conditions were used. This allows the product of the reaction to be chosen purely on the amounts of reactant employed. When the alkyne was reacted at both ends the reaction proceeded slightly slower than is usual for an alkyne reaction, going to completion in three hours compared to the usual one. Monitoring of the reaction showed that the vast majority had reacted within the usual time scale but the reaction took longer to go to completion. This was presumably due to the much lower concentrations of alkyne around and the fact that all the alkyne had to be consumed in order for the reaction to go to completion. Even with this double reaction only a singe stereoisomer was obtained with complete selectivity on both ends of the product.

2.11 Disubstituted alkynes

As mentioned in chapter 2.1 alkynes were reactive enough to allow reaction with internal alkynes. This is unlike alkenes where no extra substitution can be tolerated within the reaction. As only two alkynes were tested in the investigations with dithianes it was decided to try a few different examples including an example with a non-symmetrical alkyne to see what selectivity would be obtained.



entry[a]	alkyne	product	yield (%)[b]	ratio (*E:Z*)
1	 **142**	 **146**	75	2:1
2	 **143**	 **147**	75	>20:1
3	 **144**	 **148**	76	>20:1
4	 **145**	 **149**	67	>20:1

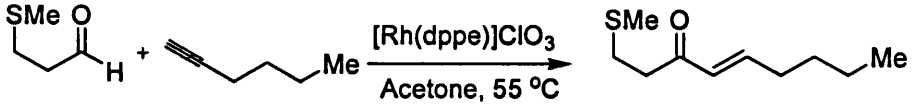
[a] Reactions carried out with 5 mol% catalyst at 55 °C for 16 hours, [b]isolated yields

Table 32: Reactivity of internal alkynes

As can be seen in table 32 the reaction with internal alkynes were once more successful. The two alkynes previously used with dithianes gave very similar results with 3-methylthio propionaldehyde **61**. Once again complete *E* selectivity was obtained from the diol **143** while almost no selectivity came from the di-ester **142**. This reinforces the theory that in this case solely a *syn*-elimination pathway cannot be the only mechanism and this would be something to investigate in the future. The electron-neutral 2-butyne **144** also gave complete selectivity for the *E* isomer in good yield. Perhaps the best result however, despite the slightly reduced yield, came from 1-phenyl-1propyne **145** which also gave a completely selective reaction both for *E* selectivity and the regioselectivity with no observation of the other regioisomer seen. This is very encouraging as it indicates that if the groups on the alkyne are different enough it may be possible to predict the product and only gain a single stereoisomer despite the four possible outcomes.

2.12 Catalyst loadings and temperature

At this point we wanted to investigate the limits of the reaction. Although the alkynes reactions are routinely allowed to react for 1 hour a close watch of the progress of the reaction with 1-hexyne **119** was made by TLC and the reaction appeared to have gone to completion within 15 minutes with an equivalent yield (95 % confirmed by ^1H NMR). This again shows the reactivity of the alkynes is significantly better than that of the alkene substances tried. As can be seen a reduction to 5 mol% catalyst is easily tolerated with alkynes with reaction times of 1 hour. Although this loading is reasonable it is obviously important to reduce the amounts of the rhodium catalyst to a minimum due to its high cost. Reactions were therefore attempted at 1 mol% and 0.1 mol% using the best alkyne, 1-hexyne.



entry	cat mol. %	time (h)	temp. °C	yield (%)[a]
1	5	1	55	98
2	1	17	55	81
3	0.1	36	55	78
4	5	1	23	93

[a] isolated yields

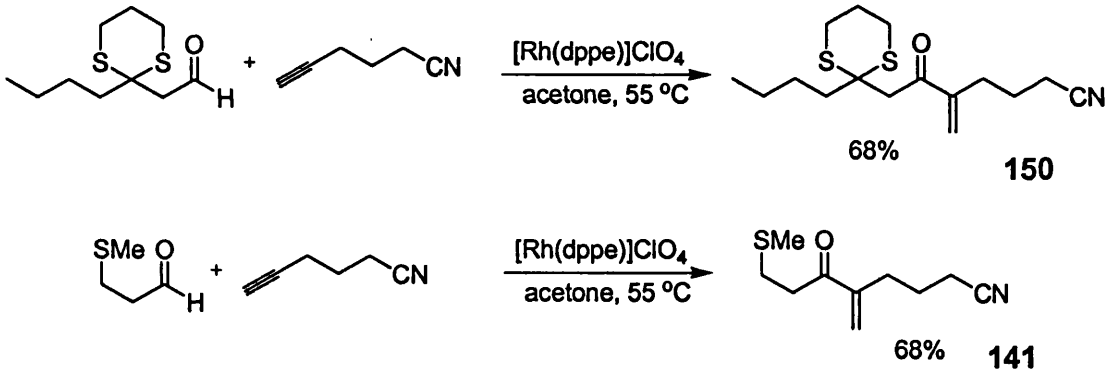
Table 33: Effect of catalyst loading and temperature on reaction time

Pleasingly both reactions did go to completion however taking significantly longer than at 5 mol% (17 hours for 1 mol% and 36 hours for 0.1 mol%). Compared to the results obtained lowering catalyst loadings with the dithiane and methyl acrylate the reaction times for the alkynes are still significantly lower than the equivalent tests (17 hours for 1 mol% with the alkyne to 48 hours with methyl acrylate). The fact that the level of catalyst can be reduced ten times lower than the lowest possible result with alkenes again reinforces the reactive nature of alkynes within this system. This is an important result as it makes the process more realistic should a larger scale reaction be needed.

As previously mentioned the alkene reactions are temperature dependant but due to the high reactivity of the alkynes a room temperature reaction (again with 1-hexyne, table 33, entry 4) was attempted and surprisingly went to completion in the same one hour time scale as the 55 °C reaction. Closer monitoring of the reaction indicated that the reaction in fact went to completion in 30 minutes. This was unexpected and a clear indication of the speed of the system.

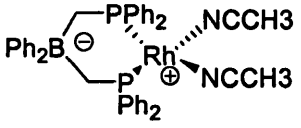
2.13 Nitrile directing effect

The one unusual substrate tried in the system was the alkyne with a terminal nitrile group. With both the dithiane and 3-methylthio propionaldehyde an 'exo' or branched product was formed.



Scheme 59: Reaction of 5-hexynenitrile with β-substituted aldehydes

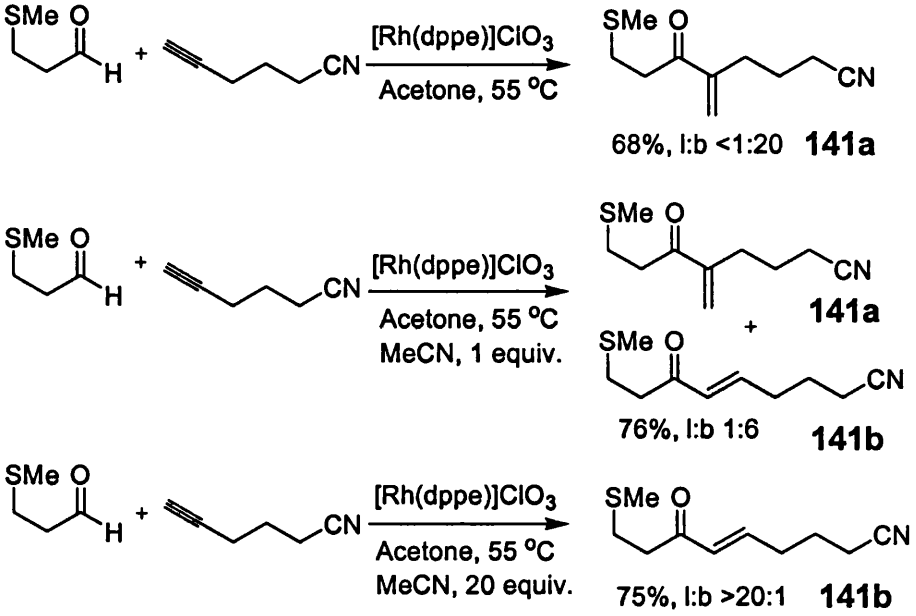
This is highly abnormal as only this single isomer was formed, again in good yield. As the only apparent difference was the CN group it was assumed that this was in some way coordinating to the rhodium catalyst and directing the reaction to this product. This is highly unusual as although there are known examples of rhodium catalysts with CN ligands (e.g. Figure 7 **151**)[120] we were only able to find limited reports of a remote nitrile group acting as a directing group in a catalytic reaction.[121, 122]



151

Figure 7: Example of a catalyst used for hydroacylation containing acetonitrile ligands

To see if it was likely, as we assumed, that the nitrile group could be coordinating the rhodium centre the same reaction was attempted this time doping the reaction with acetonitrile. This was done in two ways; one equivalent and 20 equivalents of acetonitrile with respect to the catalyst (Scheme 60).

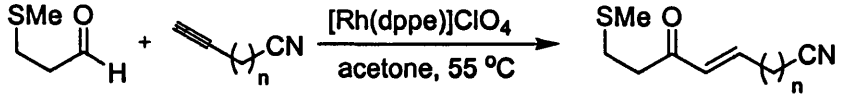


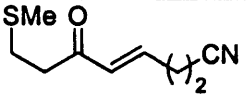
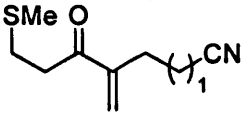
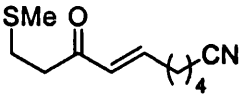
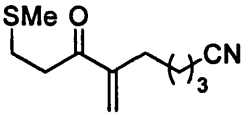
Scheme 60: Effect of acetonitrile on the stereoselectivity of 5-hexynenitrile in the hydroacylation reaction

As can be seen, in the above scheme, the addition of acetonitrile had a dramatic effect on the products isolated from the reaction. Simply adding one equivalent of the acetonitrile compared to the catalyst (so 5 mol% compared to the aldehyde and 2.5 mol% compared to the alkyne) gave a major switch from the linear to branched product. It was possible to isolate 65% of the linear product and 11% branched after one hour reaction time. This is a very interesting result as it shows how well the acetonitrile must bind to the catalyst in the place of the alkyne. With twenty equivalents of acetonitrile solely the linear products were observed. In this case the reaction took longer to go to completion (four hours compared to the usual one hour). This is presumably because the acetonitrile binds to the catalyst well and so blocks the coordination sites for the aldehyde slowing the rate of oxidative addition. The yields obtained for the reaction were equivalent, however, indicating the acetonitrile presumably did not cause degradation of the catalyst or stopped the reaction altogether. This is a nice way of choosing which isomer is formed with the simple

addition of a small amount of what is commonly used as a solvent. An attempt at carrying out the reaction using acetonitrile as a solvent gave no reaction at all even after prolonged reaction times (24 hours). This must be because of an even more pronounced effect as that observed with 20 equivalents of MeCN. As the MeCN is in such a large excess the catalyst is much more likely to bind with the MeCN than the aldehyde or alkyne and so the reaction will not proceed.

What is also strange is the size of the chelate ring that would have to be employed for the nitrile group to be coordinating to the rhodium catalyst although we were unable to determine if the coordination was occurring through the lone pairs on the nitrogen or the triple CN bond. In either case a very large chelate ring would be formed. As all of the isolated product was found to be the exo-form even in the crude reaction mixture it does appear that this chain length is good for realising this directing effect. It is however possible that any chain length would be equally as good for the reaction and merely the presence of the nitrile group is required. To see if the chain length made a difference to the effect, alkynes with one carbon atom more and one less between the alkyne and nitrile were synthesised, from the corresponding chloro-alkynes, and tried in the reaction.

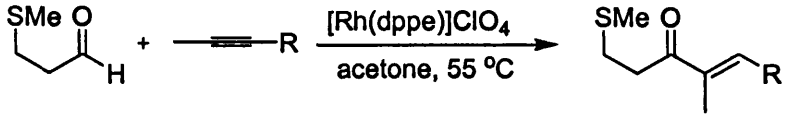


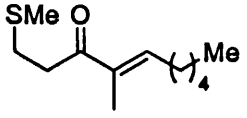
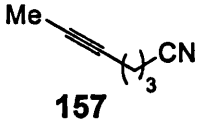
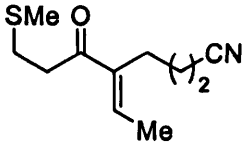
entry[a]	n (yield of alkyne)	l:b ratio	product linear	product branched	yield linear (%)[b]	yield branched (%)[b]
1	2 (87%) **152**	1.5:1	 **154b**	 **154a**	46	31
2	4 (92%) **153**	1.5:1	 **155b**	 **155a**	49	32

[a] Reactions carried out with 5 mol% catalyst for 1 hour, [b] isolated yields

Table 34: Effect of chelate size in nitrile directing effect in HA reactions.

As can be seen in table 34 (above) both alkynes reacted successfully. Neither alkyne gave solely the branched product observed with the original alkyne but both gave a mixture of the branched and linear products. This seems to indicate that the original alkyne had the ideal chelate size for the reaction to occur. The fact that a large percentage of the isolated product was the branched isomer is still in itself significant as none of this isomer was observed with any other alkyne tested. Given these positive results we were also interested in seeing if this directing effect could withstand the additional complication of being an internal alkyne. An equivalent alkyne to 5-hexynenitrile, which gave completely selective results, but with a methyl group on the other end of the alkyne was synthesised **157**. To give a good comparison oct-2-yne **156** was also tried in the reaction. The reaction with oct-2-yne was important as it was undetermined how selective this alkyne would be. All the other disubstituted alkynes which had been tested in the reaction and proved to be highly selective had large differences of both sterics and electronics between the two ends of the alkyne. In this case there is very little difference between the two groups and so high selectivity was not expected.



entry[a]	alkyne	Product	ratio l:b	yield (%)
1	 **156**	 **158**	3:1[b]	58[c]
2	 **157**	 **159**	1:3.5[b]	70[d]

[a] Reactions carried out with 5 mol% catalyst at 55 °C for 16 hours [b] Determined by ^{1}H NMR, [c]Isomers inseparable by column chromatography, [d] Isolated as branched compound (above) 53% and linear 27%.

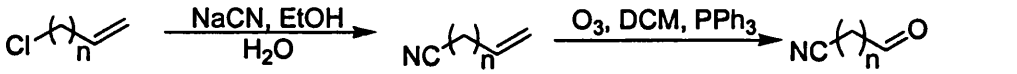
Table 35: Scope of nitrile-directing effects in alkyne HA reactions.

The level of selectivity observed for oct-2-yne is surprisingly good given the relatively small differences between the two groups at either end of the alkyne (entry 1, Table 35). A ratio of 3:1 in favour of the linear *E*-isomer was obtained. This major

product agreed with the stereochemistry obtained form the terminal alkyne and all other examples of terminal and internal alkynes tested. Interestingly the results from the CN substituted version gave almost the exact opposite of these results. A 3.5:1 ratio in favour of the branched product was obtained indicating that the directing effect is still in force when extra substitution is present. Although this results was not purely the single stereoisomer unlike the mono-substituted example the fact that the selectivity was switched to such a high degree provides good evidence of the strength of this interaction.

2.2 CN-aldehydes

Given the strength of the interaction between the CN of the alkyne it was proposed that an aldehyde with a CN group may be able to perform the chelation role fulfilled by the sulfur atom. As it was not known if the same chelate length which was most favourable for the sulfur atom would also be true of the CN a range of aldehydes were synthesised with different chain lengths. Given the extremely long chelate that must have been formed in the alkyne example the larger aldehydes were expected to perform better. The aldehydes were synthesised from the corresponding alkenyl bromides or chlorides with NaCN and subsequently treated to ozonolysis conditions to create the aldehydes (Scheme 61). Both these steps gave good yields and reasonable reaction times.

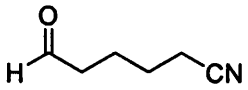
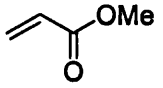
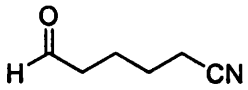
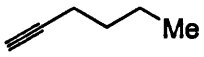
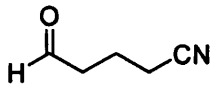
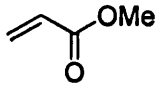
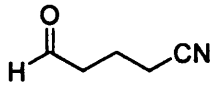
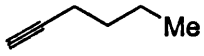
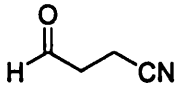
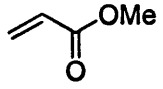
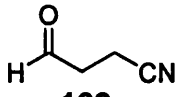
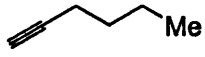


n = 2 90%	**160**	n = 2 87%	**163**
n = 3 91%	**161**	n = 3 81%	**164**
n = 4 95%	**162**	n = 4 84%	**165**

Scheme 61: Synthesis of CN-aldehydes

As can be seen three aldehydes were synthesised and each were tried in the hydroacylation reaction both with methyl acrylate and 1-hexyne to see if any hydroacylation products could be observed. Unfortunately no reactivity at all was seen despite increasing the catalyst loadings to 10 mol% and leaving the reactions for 48 hours (Table 36). Only starting materials were obtained at the end of the reaction

there was no obvious decarbonylation products however it is likely that these would be highly volatile and only small amounts would be formed so it is possible they were present just not observed.

entry	aldehyde	overall yield of aldehyde	alkene/alkyne	time[a] (h)	yield[b] (%)
1	 **165**	80 %		48	0
2	 **165**	80 %		48	0
3	 **164**	74 %		48	0
4	 **164**	74 %		48	0
5	 **163**	78 %		48	0
6	 **163**	78 %		48	0

[a] Reactions carried out with 10 mol% $[Rh(dppe)]ClO_4$ catalyst at 55 °C [b] Determined by ^1H NMR,

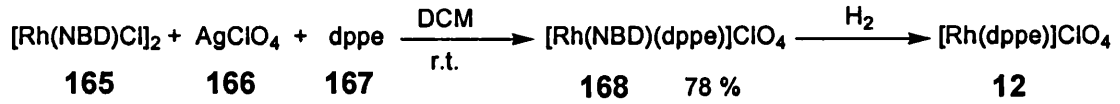
Table 36: hydroacylation reaction of CN-aldehydes

Although these results are not promising it is possible that the range of aldehydes synthesised did not include the one with the correct chelate size. Given the evident reaction with the CN-alkyne it is possible that further work in the future may identify an aldehyde in this range that is a suitable substrate for hydroacylation reactions.

Chapter 3: New Catalyst system

3.1 Development of a new catalyst system

The advances in the hydroacylation system reported so far (chapter 2) have increased the scope of both the aldehyde and unsaturated C-C components. Despite this little mechanistic information has been obtained, including any proof that the sulfur binds to the rhodium centre, other than the observed reactivity of the system. In all these reactions the catalyst itself has appeared to be the limiting factor in improving the technique. The dppe catalyst **12** does have many good qualities, it seems to be highly reactive in the hydroacylation system and there do not appear to be any appreciable problems with decarbonylation. However, rhodium is amongst the most expensive elements within the periodic table and although we have demonstrated the possibility of low catalyst loadings, before any reaction can take place the catalyst must be pre-formed from commercially available precursors, inevitably leading to some wastage of rhodium. The catalyst is prepared following the procedures reported by Bosnich (scheme 61).

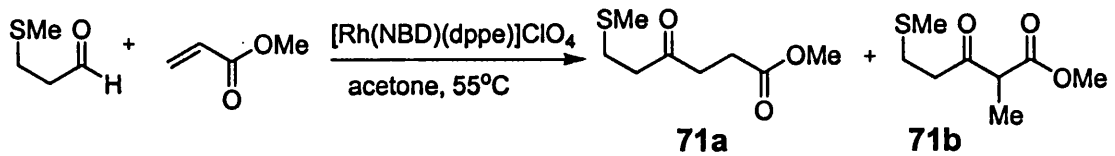


Scheme 61: Synthesis of [Rh(dppe)]ClO_4

In addition to this the catalyst should ideally be stored under argon at low temperatures as decomposition to a less, or inactive, catalyst can easily occur. This can be a real problem with the more sensitive reactions as there is little visible change to the catalyst when it starts to decompose. Another problem that has been regularly encountered occurs during activation of the catalyst. Each time, before a reaction can be initiated, the pre-catalyst must be activated by bubbling hydrogen through a solution of the pre-catalyst. This activation is monitored by following the colour change of the solution. In DCE the colour change is very slight; light orange to dark yellow, and can often only be spotted with practise. Switching the solvent to acetone has made an improvement as the colour change is more defined, however problems can still occur. This makes the reaction less than user friendly especially to those unfamiliar with rhodium catalysts. If the catalyst is not completely activated

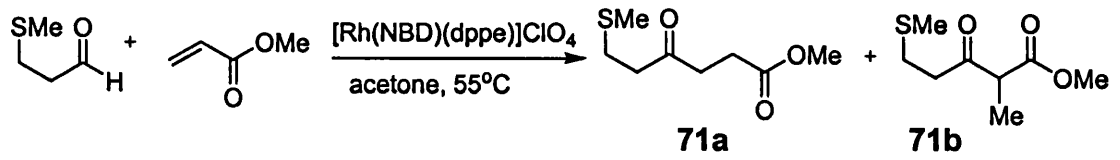
obviously less is available for the reaction. When the active catalyst is formed it is highly unstable, less so in acetone than DCE, and decomposes very rapidly if exposed to air or water. Once activated monitoring the catalyst by ^{31}P NMR shows a large number of peaks quickly appearing, indicating the formation of multiple species. For this reason a long activation step is also a problem as it allows more time for the catalyst to decompose. Once the substrates have been added to the system the catalyst becomes more stabilised. Another major disadvantage with this catalyst is that only alkenes that are mono-substituted with highly electron withdrawing groups can be successfully used (acrylates and acrylamides). A small amount of product is obtained from the reaction with 1-octene and the methylthio propionaldehyde (**61**) but despite lengthening reaction times and increasing catalyst loadings, only 20 % product could be isolated.[84] No reactivity at all was observed between 1-octene and dithianes, even the unsubstituted versions, or with the substituted sulfide aldehydes. There are also problems with the less reactive substrates often not always going to completion presumably due to the catalyst decomposing. This may be a result of decarbonylation or could be a degradation of the catalyst in another way. We are aware that once activated the catalyst is particularly sensitive to air but have been unable to fully characterise any decomposition products.

It was assumed that the catalyst needed to be activated before any reaction would take place, based on previous work and the original work performed by Bosnich.[19, 20] However, the reaction had not been attempted without the activation step and it was deemed important to establish if this was in fact necessary. For all the following experiments a test system using 3-methylthio propionaldehyde and methyl acrylate was used, as this reaction goes to completion in a reasonable time scale. A reaction was therefore tried using these substrates with 5 mol% [Rh(NBD)(dppe)]ClO_4,**168** with no activation, in acetone at 55 °C (Scheme 62).



Scheme 62: Reaction using non-activated catalyst

To our surprise this reaction did go to completion, taking a longer time (three hours compared to ninety minutes) than when the catalyst was activated. This was a significant advantage as it removed the need for hydrogen activation from the reaction. This presumably indicates the substrates bind strongly enough to displace the NBD group. This simple improvement would allow the reaction to take place on a larger scale much more safely and easily. As at this point the catalyst was still being pre-formed, a subsequent one pot reaction was tried in which the rhodium source **165** dppe **167** and silver perchlorate **166**, all used to make the pre-formed catalyst, were mixed together in acetone and then the reactants added. Again this reaction was successful, although taking longer again to go to completion (four hours) (Scheme 63). This was a good result, as it proved the catalyst did not need to be isolated before use but could be made and used *in-situ* avoiding any storage problems. All the reactants used for the one-pot catalyst system are commercially available and not as air sensitive as the isolated catalyst, allowing easier storage. This advancement additionally made the exploration of the system much easier as new catalysts did not have to be pre-formed before being trialled allowing a much larger range of ligands to be investigated.

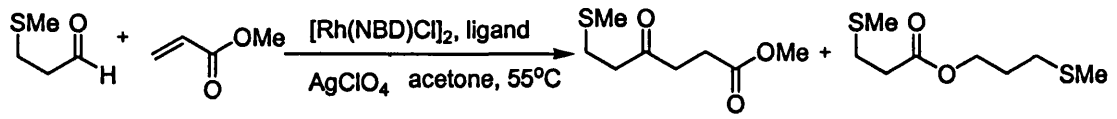


71a **71b**

75% yield 4:1 a:b

Scheme 63: Reaction with *in-situ* catalyst formation

To explore if this one-pot method could be improved to levels as good as or better than the original catalyst system, different components were investigated. A range of ligands were screened to check for reactivity in the hope of improving the timing back to or better than the levels achieved with the preformed and activated dppe catalyst. Amongst those ligands tested mono-dentate ligands were screened to see if they provided any additional reactivity. A range of *bis*-phosphines were also explored including ones with oxygen linkers as it was reasoned that if the catalyst could provided additionally chelating stabilisation a more robust catalyst would be formed and hopefully give additional reactivity (Table 37).



entry[a]	ligand	time (h)[b]	conversion to hydroacylation products (%)[c]	Conversion to Tischenko product (%)[c]
1	Triphenylphosphine **169**	1	0	100
2	Tricyclohexylphosphine **170**	4	0	100
3	JOSIPHOS **171**	0.5	0	100
4	QUINAP **172**	8	0	100
5	dppe **167**	4	100	0
6	dppp **173**	3.75	100	0
7	dppb **174**	4	100	0
8	dppf **175**	48	0	0
9	BINAP **28**	8	100	0
10	Tol-BINAP **64**	48	70	0
11	Me-Duphos **29**	24	100	0
12	DIOP **176**	48	80	0
13	Xantphos **177**	48	0	0
14	DPEphos **178**	2	100	0

[a]Reactions carried out with 2.5 mol% $[Rh(NBD)Cl]_2$, 5 mol% ligand and 5 mol% $AgClO_4$ [b] Reactions monitored by TLC, [c] Determined by ^1H NMR

Table 37: Effect of varying ligands on the hydroacylation reaction

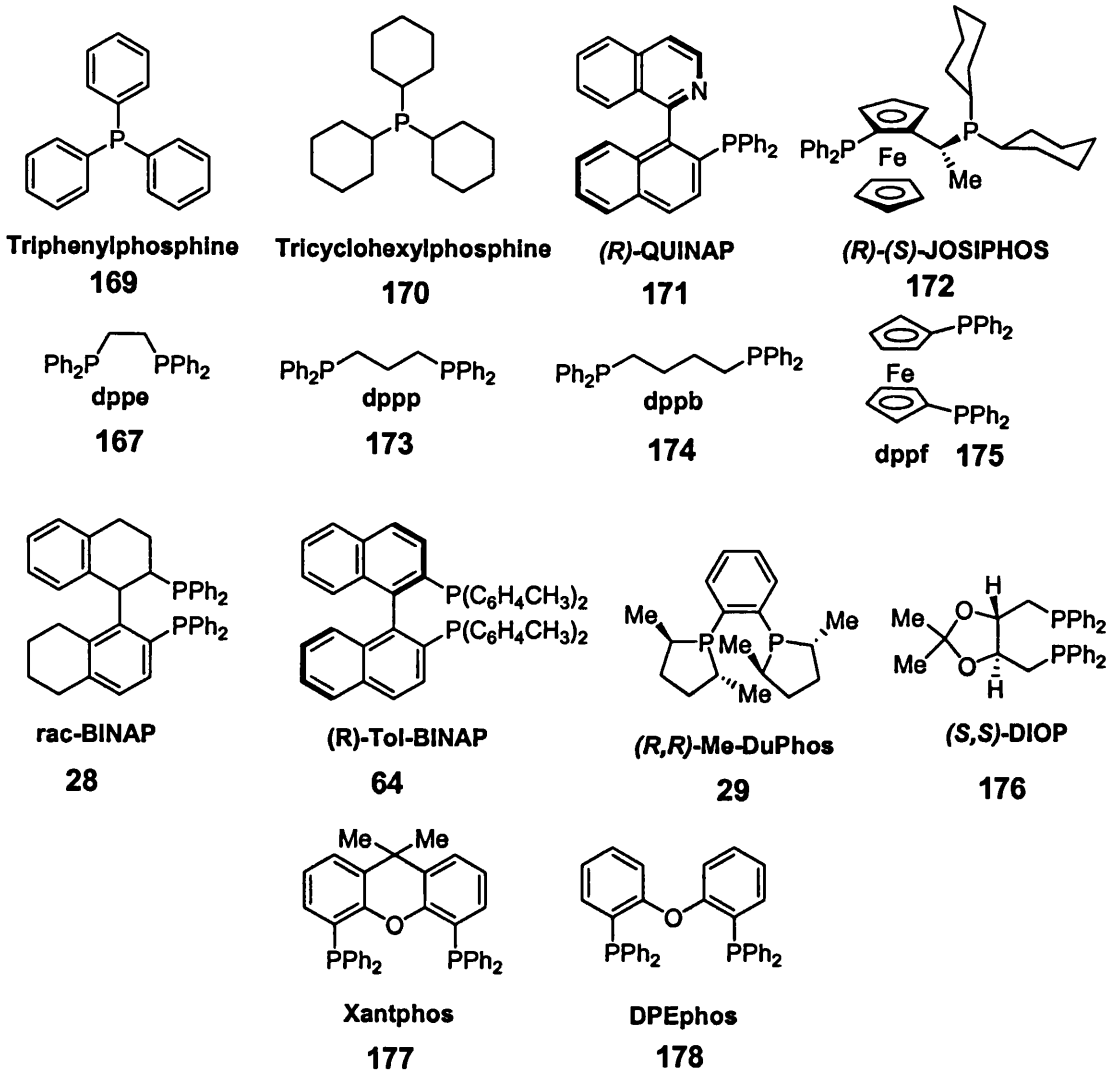
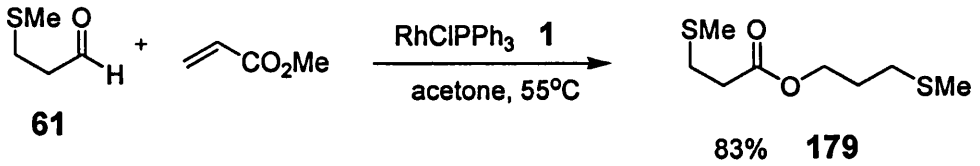


Figure 8: Ligands used during the screen for a more reactive catalyst system

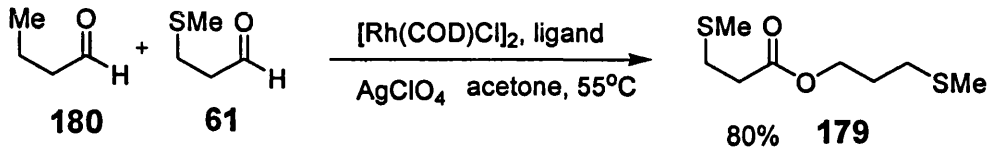
As can be seem from table 37 a number of interesting results were obtained. Mono-dentate ligands and those with hemi-labile systems seem to be particularly good at catalysing a Tischenko reaction of the 3-methylthio propionaldehyde (scheme 64).



Scheme 64: Tischenko reaction of 3-methylthio propionaldehyde

This was at the expense of the hydroacylation reaction, the products of which were not observed at all in these systems. This reaction to the Tischenko product can be performed with the original dppe catalyst **12** if no olefin is added to the reaction

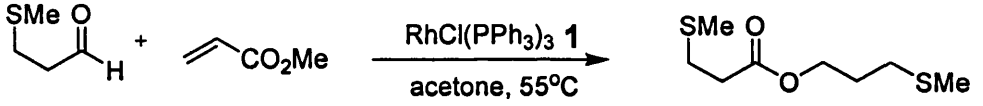
mixture going to completion in eighteen hours.[84] The Tishchenko reaction for these new catalysts was particularly fast, going to completion within 30 minutes. As this is in itself an interesting observation an attempt at catalysing a cross Tishchenko reaction was attempted with the sulfide aldehydes and butyraldehyde **180**. This reaction was unsuccessful with again only the product from the 3-methylthio propionaldehyde being obtained.



180 **61** 80% **179**

Scheme 65: Reaction of butyraldehyde and 3-methylthio propionaldehyde

This result indicates the reactivity of this aldehyde with these rhodium catalysts. Although many groups, including the Jun group,[11, 17, 72, 80, 123, 124] successfully use Wilkinson's complex **1** in hydroacylation reactions when this was tried with methylthio propionaldehyde **61** a Tishchenko reaction occurred (scheme 66). This is perhaps not surprising given that triphenylphosphine in the ligand screen also gave this result.



61 85% **179**

Scheme 66: Reaction catalysed by Wilkinson's complex

Other ligands were more successful as hydroacylation catalysts. The range of ligands in the dppe series were all successful at giving hydroacylation products. These ligands did not give any obvious benefit in terms of timing to the reaction with all of them going to completion in approximately the same time frame as dppe itself. One exception to this is DPPF which did not give any reaction at all. This may be due to some kind of interaction from the iron or simply a reflection of the large amount of steric bulk around the ligand.

Other *bis*-phosphines were also reactive in the hydroacylation system. None of the *bis*-phosphines screened gave any indication of the Tischenko product which explains why it was not observed with the original catalyst system when an olefin was present. Most of these phosphines reacted successfully in the hydroacylation system, however the times taken to go to completion varied significantly depending on the ligand. BINAP **28** went to completion in 8 hours, longer than dppe, and Tol-BINAP **64** did not fully go to completion even after reaction for 48 hours. Both these ligands have fixed bite angles and large amounts of steric bulk around the phosphine ligand, Tol-BINAP more than BINAP **28**. This increased steric bulk may be the reason that the ligand **64**-catalyst systems take longer to go to completion than the original dppe system. Equally, although both Me-Duphos **29** and DIOP **176** gave the correct product the reaction times were longer than with the dppe ligand. Xantphos **177** and DPEphos **178** despite being closely related gave very different reactivity. Xantphos did not give any reaction at all even after 48 hours while DPEphos gave the highest level of reactivity going to completion in 105 minutes, the same time frame as observed with the original activated catalyst system. We theorised that this extra level of reactivity could be attributed to the oxygen atom within the DPEphos partially binding to the catalyst centre when required, stabilising the activated catalyst (Figure 9).

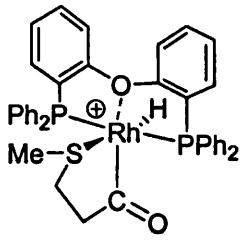
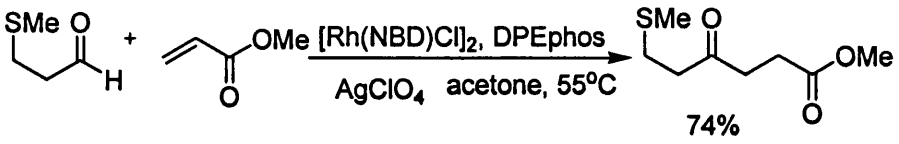


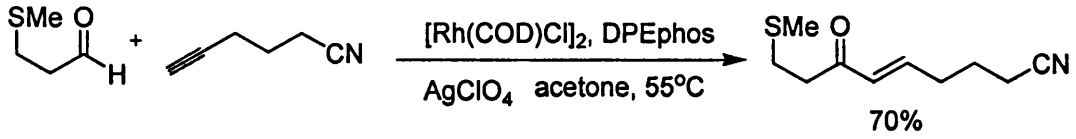
Figure 9: Coordination of the O atom of DPEphos to the metal-acyl intermediate

Xantphos is much more rigidly held than DPEphos and this may be why this does not work in the reaction. It is possible that the conformation it is held in does not allow the phosphines to bind efficiently at all stages of the catalytic cycle to the rhodium. Even more so than BINAP, Xantphos is very constrained in its conformation and this may be a key reason why the ligand is not successful in the reaction. Interestingly, with DPEphos none of the branched product was observed (scheme 67). This must also be due to some effect that the DPEphos has over the dppe ligand. This allows much cleaner reactions and hence reduces the difficulties of purification.



Scheme 67: Stereoselectivity of DPEphos ligand

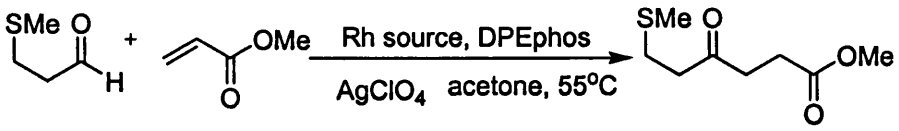
When the reaction using DPEphos was tried with the CN-alkyne that had previously been shown to give a branched product (Chapter 2, scheme 58) solely the linear product was obtained (Scheme 68).



Scheme 68: Reaction of DPEphos catalyst with CN-alkyne

It therefore seems reasonable to assume that in the same way that acetonitrile is able to block the coordination of the nitrile group and lead to a linear product, the DPEphos (presumably through the oxygen atom) is equally able to perform this role. This may be at least part of the reason that the methyl acrylate reaction gives only the linear product.

To further increase the reactivity of this new catalyst system the other components were also varied. Firstly the rhodium source was investigated. This makes little difference in systems where hydrogenation is used as the coordinating diene/alkene is removed at that stage. The stability of the precursors is directly related to the diene/alkene with NBD giving much more stable pre-cursors than other possible substrates such as COD or ethylene. With the one-pot method the speed of the reaction is in part probably governed by how quickly the substrates can displace the diene/alkene so the weaker the coordination, the quicker the reaction should be. To see if this was the case a series of experiments starting with $[Rh(NBD)Cl]_2$ **165**, $[Rh(COD)Cl]_2$ **8**, $[Rh(COE)Cl]_2$ **50**, and $[Rh(ethylene)_2Cl]_2$ **181** were carried out. For all these experiments the ligand used was DPEphos and the silver perchlorate counterion was employed (Table 38).



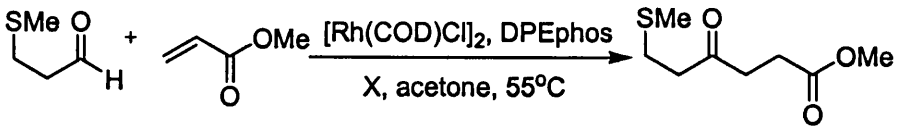
entry[a]	rhodium source	Time (h)[b]	conversion (%)[c]
1	$[Rh(NBD)Cl]_2$ **165**	2	100
2	$[Rh(COD)Cl]_2$ **8**	1.5	100
3	$[Rh(COE)Cl]_2$ **50**	2	100
4	$[Rh(ethylene)_2Cl]_2$ **181**	1	100

[a]Reactions carried out with 2.5 mol% of the rhodium source (5 mol% rhodium) 5 mol% DPEphos and 5 mol% $AgClO_4$, [b]Monitored by TLC, [c]Determined by ^1H NMR

Table 38: Effect of Rhodium source on the speed of reaction

An improvement in the speed of the reaction was recorded, although only moderate. The one unexpected result was with COE which gave a relatively slow reaction time. This may be due to the highly sensitive nature of the rhodium source which may have degraded before the reaction was attempted. Despite this anomalous result the other compounds in the rhodium series performed as expected. The quickest reaction being with $[Rh(ethylene)_2Cl]_2$ which went to completion in one hour; faster than any other system used. For ease of use coupled with the quicker reaction times it was decided to carry out further studies using $[Rh(COD)Cl]_2$ as this substrate is fairly stable unlike the ethylene or COE dimers and more reactive than the NBD substrate.

Given the high reactivity of DPEphos and the rhodium COD source an attempt was made to increase this further by modification of the other starting material namely the counterion (Table 39).



entry	Counterion X	Time (h)	Conversion (%)
1	$AgClO_4$ **166**	1.5	100
2	$AgBF_4$ **182**	1.5	100
3	$AgPF_6$ **183**	3	100
4	AgOTf **184**	2	100
5	$NaBaR^F$ **185**	24	0
6	$AgBaR^F$ **186**	3	100
7	$Ag[CB_{11}H_6Cl_6]$ **187**	0.75	100

[a]Reactions carried out with 2.5 mol% of the rhodium source (5 mol% rhodium) 5 mol% DPEphos and 5 mol% $AgClO_4$, [b]Monitored by TLC, [c]Determined by ^1H NMR

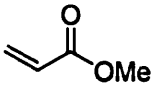
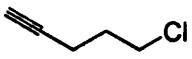
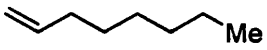
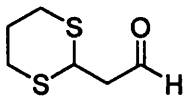
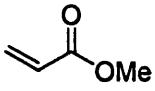
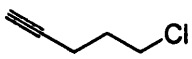
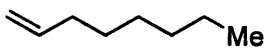
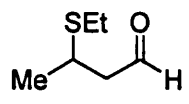
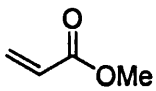
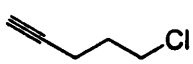
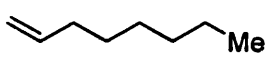
Table 39: Effect of counterions on speed of hydroacylation

As can be seen counterions do seem to have an effect on the speed of the reaction although this is much less marked than the effect from the ligands. Perhaps the most startling result was when NaBaRF **185** was used rather than the silver equivalent **186**. In this case no reaction was seen at all and the reaction was observed to go black over time. It appears that the sodium causes degradation of the catalyst to such an extent that no reaction is possible. This reinforces the need to use silver salts rather than sodium for any other reactions.

Other counterions had similar results to each other. Silver perchlorate **166**, the original counterion used, was amongst the fastest reacting along with silver tetrafluoroborate **182** which reacted in the same time frame (90 minutes). Silver triflate **184** was successful in the reaction but gave lower reactivity than the previous counterions, as did silver BARF **186**. More interestingly, a decrease in the reaction time was achieved by using a carborane counterion **187**. The chloro-carborane counterion gave completion of the reaction in only 45 minutes. This reaction is faster than any of those carried out before, showing the additional reactivity given by this combination of ligand, rhodium source and counterion. The differences observed with the various counterions may be due to how much the counterions are capable of slowing any degradation of the catalyst in the presence of air/water. It is possible that

the $[CB_{11}H_6Cl_6]$ stabilised catalyst is less prone to degradation and so helps to speed the reaction as more catalyst remains active for longer.

All the above results indicate the possibilities for gaining quick reaction times but at this stage the reactions had all been done with the same substrates; 3-methylthiopropionaldehyde and methyl acrylate. It was important to determine the scope of this new catalyst system. To that end a series of experiments were carried out with $[Rh(COD)Cl]_2$ and DPEphos. It was decided to employ $AgClO_4$ as the counterion as although not the fastest system it is commercially available and considerably less expensive than the carborane.

entry	aldehyde	alkene/alkyne	Catalyst loading (mol%)	product	time (h)	yield (%)
1			5	**71**	1.5	74
2			5	**122**	1	82
3			5	**151**	16	80
4			10	**188**	24	70
5			5	**79**	4	75
6			5	**112**	4	87
7			5	**189**	24	82
8			10	**190**	28	89
9			5	**106**	16	81
10			5	**191**	16	97
11			10	**192**	24	73
12			10	**193**	48	61

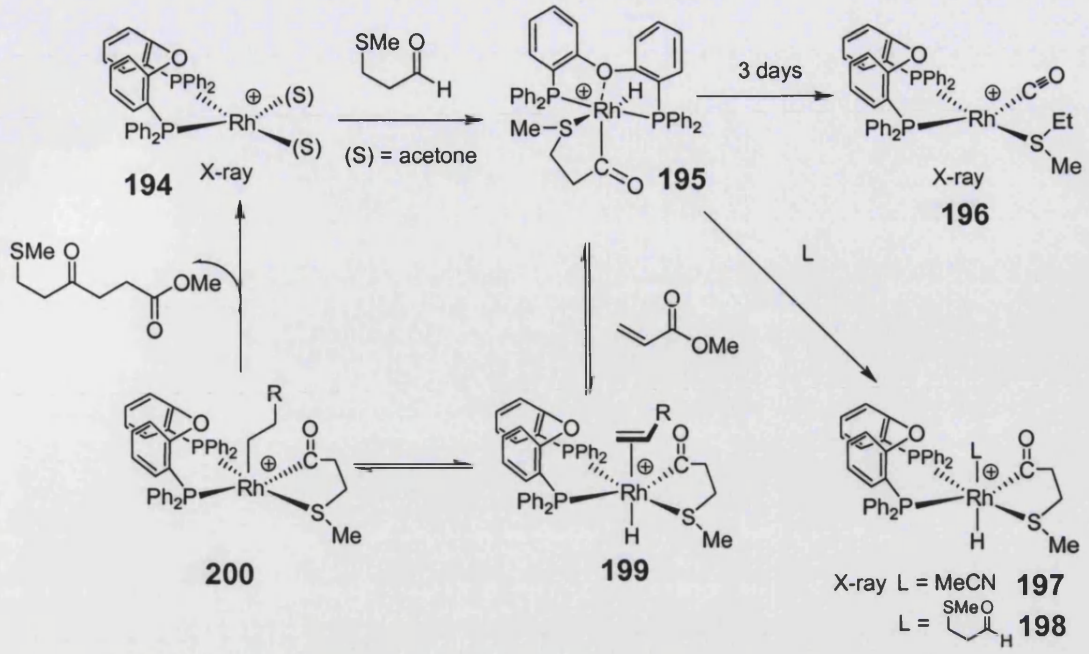
[a]Reactions carried out with 2.5 mol% of the rhodium source (5 mol% rhodium) 5 mol% DPEphos and 5 mol% $AgClO_4$, [b]Monitored by TLC, [c]Determined by ^1H NMR

Table 40: Scope of the new catalyst system

As can be seen the in table 40 the results were very successful. In all cases reactions performed previously with the dppe catalyst were as successful, or more so with the *in-situ* DPEphos catalyst. In addition to this the catalyst loadings for the dithiane and substituted sulfide could be reduced to 5 mol% for the quicker reactions with no loss of yield. Most interestingly, the reactions with 1-octene and all three aldehydes yielded product. This was despite this substrate being completely unreactive with both the dithiane and substituted sulfide previously and only moderately reactive with 3-methyl thiopropionaldehyde using the previous dppe catalyst system. This is an excellent result and it would allow for the use of many more substrates within the reaction system that had previously been considered difficult.

3.2 Mechanistic studies

Given these positive results it was decided to see if it was possible to investigate the mechanism of the reaction. As already stated at the beginning of this chapter it had not been possible to isolate a crystal structure showing the sulfur binding to the catalyst and hence acting as a chelate. The fact that the reaction works is a good indication of this happening and the additional intramolecular reaction by Bendorf also using sulfur as a chelate is also good circumstantial evidence.[28] Using this new catalyst we hoped it would be possible to gain more physical evidence of chelation. In order to do so we worked in collaboration with the Weller group to gain crystal structures to see how they are effected by the use of DPEphos as the ligand. The Weller group were able to isolate three structures within the catalytic cycle of the DPEphos ligand. These crystal structures were formed from the catalyst balanced by the carborane counterion. From these crystal structures and NMR data the catalytic cycle in Scheme 68 was proposed.[125]



Scheme 69: Proposed catalytic cycle of hydroacylation reaction

The active catalyst species $[Rh(DPEphos)(OCMe_2)_2][CB_{11}H_6Cl_6]$ (Scheme 69 **194**) was generated by hydrogenation of $[Rh(DPEphos)(NBD)][CB_{11}H_6Cl_6]$ in acetone. The crystal structure of this species was obtained (Figure 10) showing a square planar Rh(I) motif, with no close Rh···O interactions from the DPEphos ligand.

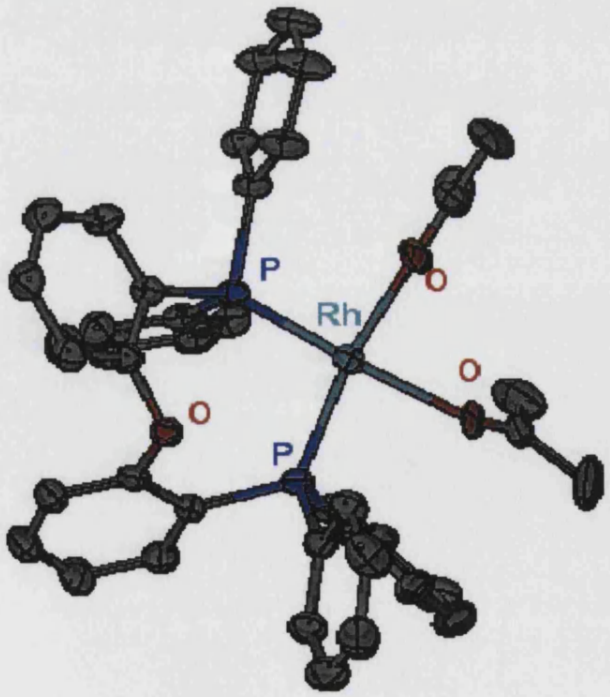


Figure 10: Crystal structure of the solvated DPEphos catalyst 194

This conclusion was supported by the solution NMR data, in particular a doublet is observed in the $^{31}P\{^{1}H\}$ NMR spectrum δ 41.8 [*J*(RhP) 209 Hz)]. Although NMR data can easily be obtained for the [Rh(dppe)NBD][$CB_{11}H_6Cl_6$] once activated with hydrogen, multiple peaks in the $^{31}P\{^{1}H\}$ spectra are found demonstrating multiple species are present. This is an indication of the stability of the two species.

When one equivalent of methylthio propionaldehyde **61** was added to **194** a complex identified by NMR as the acyl hydride [Rh(DPEphos)(H)($MeSCH_2CH_2CO$)][$CB_{11}H_6Cl_6$], **195** was immediately observed. The room temperature ^{1}H NMR spectrum obtained by the Weller group shows a broadened integral 1 H hydride signal at δ – 8.75 as a doublet of triplets [*J*(RhH) 23, *J*(PH) ~1], and a doublet in the $^{31}P\{^{1}H\}$ NMR spectrum. This data indicates that a fluxional process must be occurring at room temperature. This is not the case when the solution is cooled to -93 °C. At this temperature the $^{31}P\{^{1}H\}$ NMR shows tightly coupled AB systems with *trans* PP coupling, at δ 26.8, 25.9 [*J*(RhP) 125, *J*(PP) 303]. The ^{1}H NMR spectrum reveals a single hydride resonance at δ – 8.62 ppm that shows *cis* coupling to phosphorus. This data indicates **195** probably has the DPEphos coordinating *mer* to the metal, perhaps with a coordinated oxygen. *Trans* spanning DPEphos with a coordinated have been reported.[126] It is likely the hydride is opposite the sulfur as it is improbable it resides opposite to the high *trans*-influence acyl ligand. A relatively large *J*(RhH) coupling constant [23 Hz] is consistent with this. It is possible a 5-coordinate intermediate with an unbound oxygen atom is responsible for the fluxional processes observed at room temperature although additional work would be needed to confirm this theory. Compound **195** does not readily decarbonylate ($t_{1/2}$ 24 hrs), although after 3 days conversion to the decarbonylated product **196** is observed, and attempts to recrystallise **195** led to the Weller group isolating the decarbonylated product **196** (Figure 11).

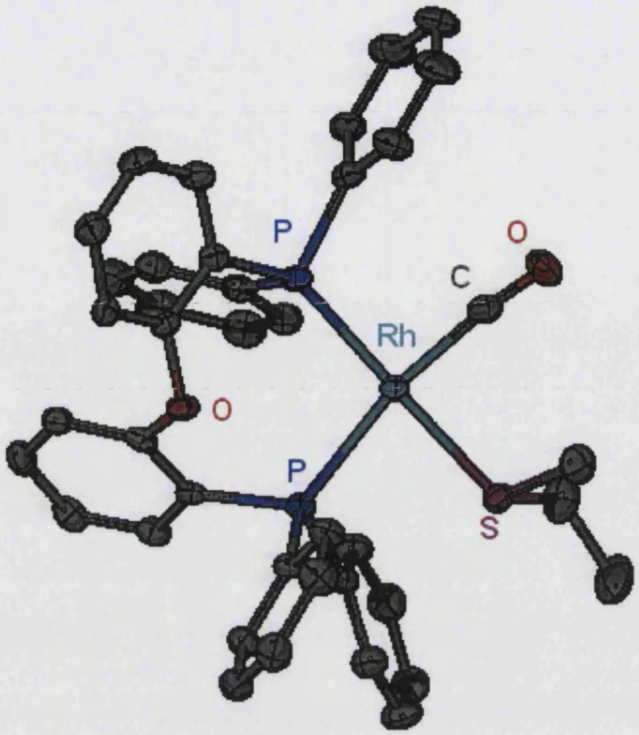


Figure 11: Crystal structure of decarbonylated product 196

This result is in contrast to the activated dppe catalyst, which has a half life of around 20 minutes and has fully decomposed within one hour to a mixture of products one of which is the product of decarbonylation, $[Rh(dppe)(CO)(SMeEt)][CB_{11}H_6Cl_6]$. These observations lend strength to the argument that the DPEphos ligand is assisting in stabilising this intermediate.

It is apparent that the oxygen atom from the DPEphos ligand can easily decoordinate as addition of a slight excess of acetonitrile or 3-methylthiopropionaldehyde **61** to **195** results in the instant formation of $[Rh(DPEphos)(L)(H)(MeSCH_2CH_2CO)][CB_{11}H_6Cl_6]$ L = MeCN, **197** L = methylthiopropionaldehyde **(61) 198,** in which the oxygen is no longer bound. The crystal structure of **197** (Figure 12) was obtained. This crystal structure is the first solid evidence of the ability of the sulfur atom in 3-methylthio propionaldehyde **61** to act as a chelate to the rhodium. NMR data suggest two closely related complexes in solution.

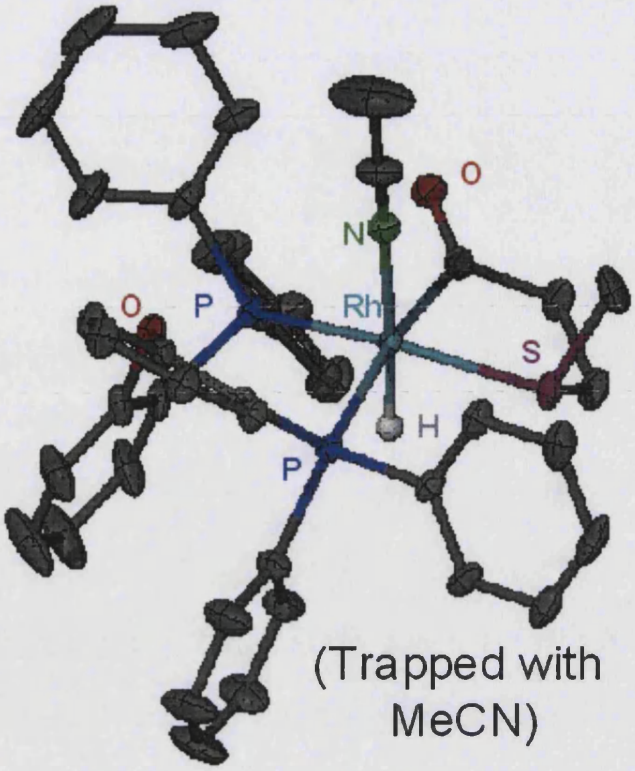
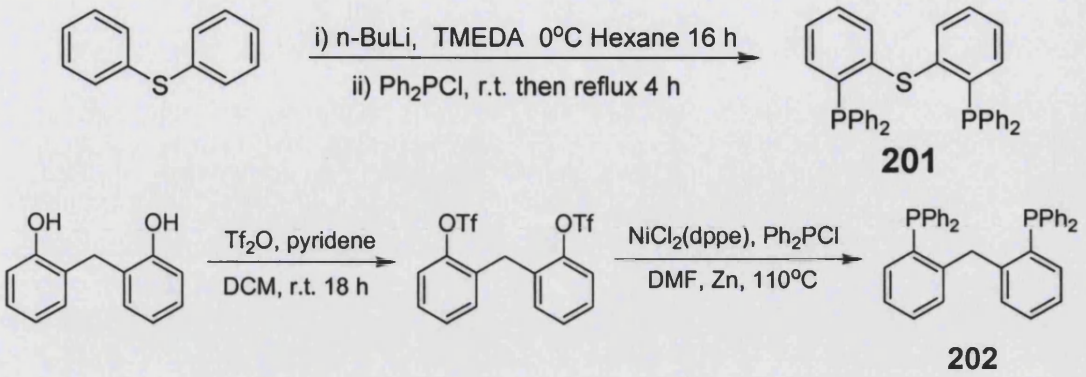


Figure 12: Crystal structure of metal-acyl intermediate 174 stabilised with MeCN 197

195 and **197** can enter directly into the catalytic cycle, as addition of alkene (methyl acrylate) immediately results in the hydroacylation reaction producing product, proving this is a reasonable model. Acyl-hydrido rhodium complexes resulting from addition of simple aldehydes are rare[127-131] as decarbonylation usually leads to only the decarbonylated product being isolated. As far as we are aware **195** and **197** represent true examples (rather than model systems) of these species, also competent for the catalytic hydroacylation of useful substrates.[16] These complexes have often been suggested, but not experimentally observed. Presumably the DPEphos ligand temporarily blocks a vacant site on **195** necessary for decarbonylation[132, 133] while being able to move aside to allow the coordination of substrate, while in **197** the acetonitrile fulfils this role. This crystal structure is the first conclusive evidence that the sulfur is able to chelate to the rhodium and infers that in doing so it stabilises the catalyst to decarbonylation.

This hypothesis is supported by varying the ligand (changing the coordinating properties) to observe the effects. To this end two further ligands were synthesised

the first with a sulfur atom in place of the oxygen and the second with a carbon atom in this position.



Methylene bridged ligand synthesis carried out by RL Woodward

Scheme 70: Synthesis of thioether ligand and methylene-bridged ligand

[Rh(**201**)(NBD)][$CB_{11}H_6Cl_6$] **203** (Figure 13) is isolated when the thioether ligand **201** is used. In this complex attempts to remove the NBD group with H_2 failed as the sulfur binds so strongly the resulting complex is a stable 18-electron species.

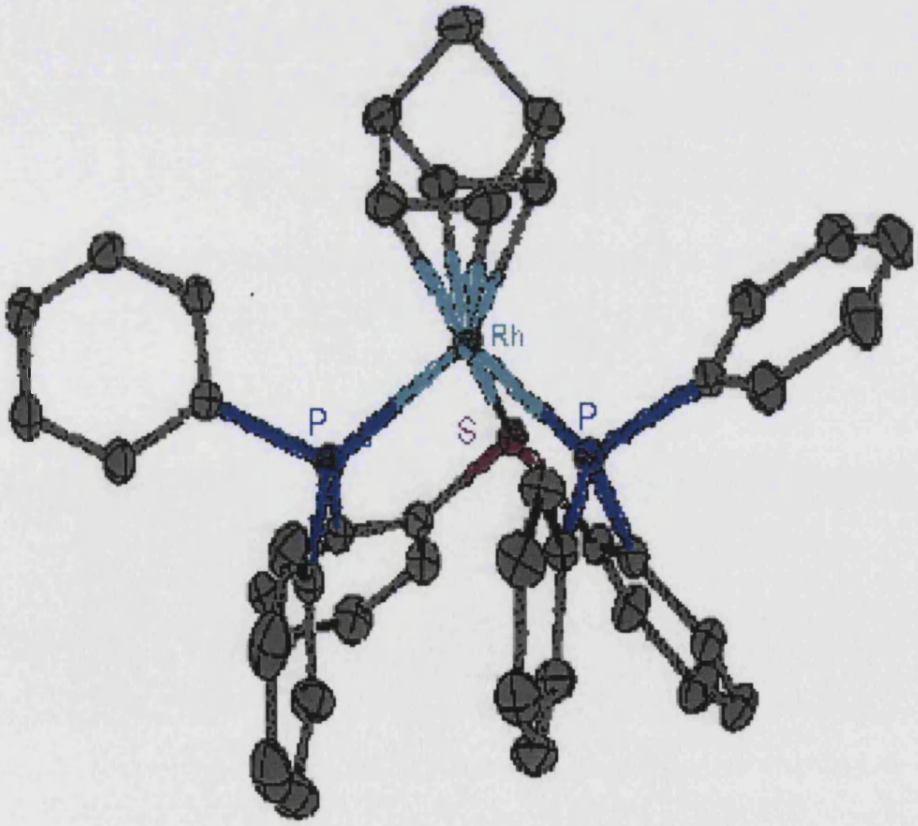


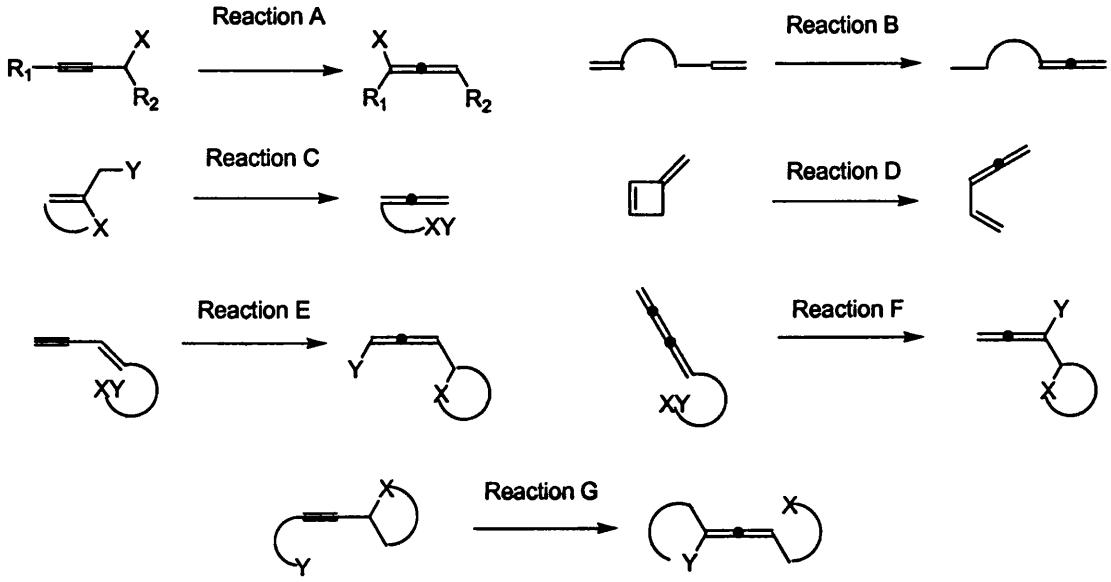
Figure 13: Crystal structure of [Rh(**201**)(NBD)][$CB_{11}H_6Cl_6$] **203**

The methylene-bridged ligand, **202**, had the opposite effect. In this case the ligand would be unable to provide any additional stabilisation but easily forms the complex [Rh(**202**)(acetone)$_2$][$CB_{11}H_6Cl_6$] **204**. However, addition of aldehyde **61** leads to very rapid (5 minutes) decomposition, with no acyl hydride intermediate observed. This may be due to CH insertion occurring within the ligand itself. Or it may be just due to the complete lack of stabilisation of the active catalyst species.

This work indicates the additional benefits given by using a catalyst based on the DPEphos system and is the first physical evidence of the sulfur atom acting as a chelate to the rhodium centre.

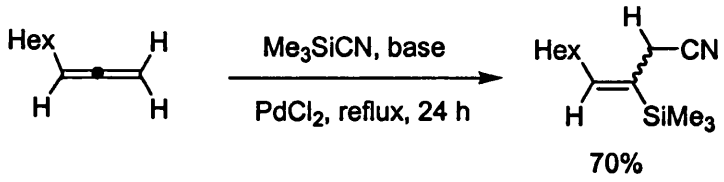
Chapter 4: Hydroacylation reactions with allenes

The good results obtained using alkenes and alkynes in hydroacylation reactions allowed a range of substrates to be used in the hydroacylation reaction. Despite this it is still not possible to create a potential chiral centre with these substrates. This is for obvious reasons in the case of the alkyne, while only monosubstituted alkenes have proved to be reactive, even with the improved DPEphos catalyst system. It was postulated that allenes with their highly reactive nature may be suitable substrates in the hydroacylation reaction. If di- or tri-substituted allenes could be successfully employed potential chiral centres would be formed. Even if optical purity could not subsequently be achieved a range of interesting non-conjugated enone products would be synthesised again expanding the utility of this process. The first allene derivative was prepared in 1887 by Burton and Pechmann but the structure was not confirmed until 1954.[134, 135] There are currently many ways of synthesising allenes including; migration of a non-cumulated π-bond into cumulation with a second π-bond such as an alkyne (reaction A, scheme 71) or conjugated or isolated diene (reaction B, scheme 71):elimination process from a ring to a π-bond (reaction C, scheme 71): the addition of intramolecular nucleophile to a conjugated alkyne-containing system e.g. 1,3-enyne (reaction E, scheme 71) or higher cumulene (reaction F, scheme 71): and substitution reactions (reaction G, scheme 71).



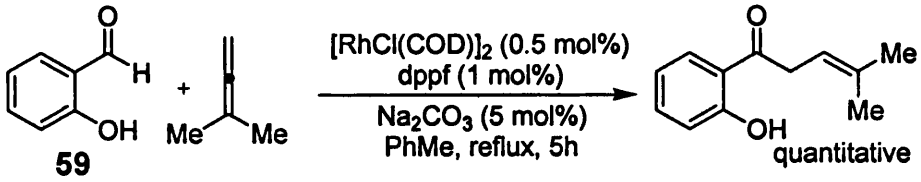
Scheme 71: Possible methods of allene synthesis[136]

Allenes have received much interest over the years as they possess a hybrid character of an olefin and an acetylene and they are capable of possessing axial chirality. More recently they have become of interest to metal catalysed reactions which had previously been unavailable due to selectivity issues. In particular, palladium catalysed reactions have enjoyed particular popularity with several reviews now available.[136-138] Amongst the reactions known are the addition of carbon and heteroatom nucleophiles and cross-coupling reactions. One early report involved the addition of trimethylsilylcyanide over a variety of allenes with palladium and nickel catalysts (scheme 72).[139]



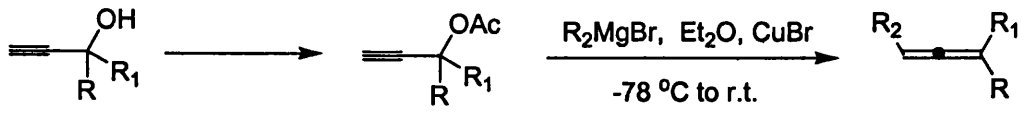
Scheme 72: Early reaction of allenes catalysed by $PdCl_2$

Allenes have also been used in hydroacylation reactions by Murai *et. al.* although only examples with substitutions on one end of the allene have been employed (scheme 73).[79]



Scheme 73: Hydroacylation of allenes

To test whether allenes would work in our system a di- and tri-substituted allene were synthesised from their corresponding alkynyl acetates. The acetates themselves were prepared from the simple protection of the appropriate propagylic alcohols with acetic anhydride (scheme 74).[140]

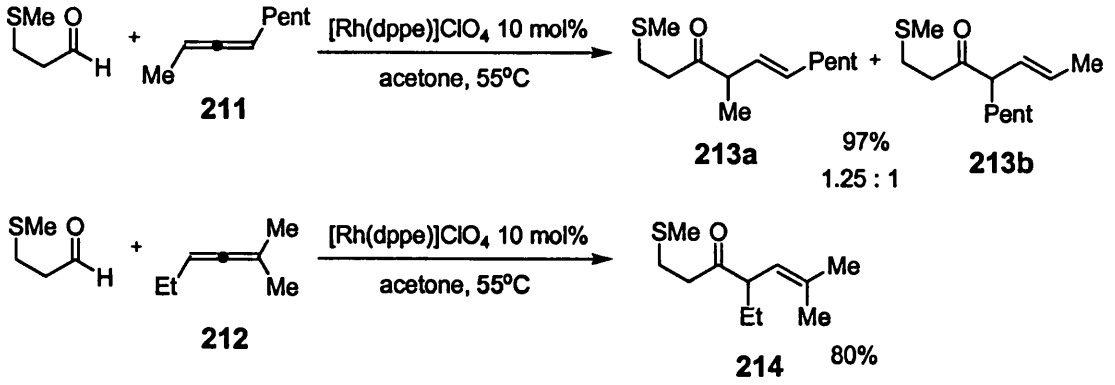


R = Me, R_1 = H	82%	**205**
R = Pent, R_1 = H	78%	**206**
R = *i*Pr, R_1 = H	75%	**207**
R = Ph, R_1 = H	79%	**208**
R, R_1 = Me	84%	**209**
R, R_1 = Cyclohexyl	78%	**210**

Scheme 74: Synthesis of allenes

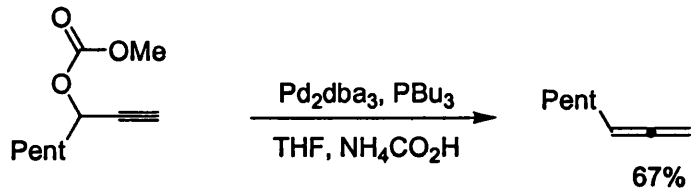
Although the acetates were prepared in good yield (70-85%) the allenes themselves had much reduced yields (40-70%). To some degree this is attributable to the high volatility of the allenes which were partially lost when removing the solvent from both the reaction and subsequent column. To help minimise this loss and due to the non-polar nature of the allenes, neat pentane was used as the solvent for purification *via* column chromatography. Despite the relatively low yields, the reactions themselves were very clean and easily scaled up to reasonable levels (2 g for example).

Once again 3-methylthio propionaldehyde **61** was used in the test reaction. The relatively high catalyst loading of 10 mol% [Rh(dppe)]ClO_4 **12** was also employed with acetone as solvent. We were pleasantly surprised to find that both the allenes tested in the reaction went to completion as monitored by TLC and NMR spectroscopy.



Scheme 75: Reactivity of allenes in the hydroacylation reaction

This was an excellent result as this was the first time we had been able to get compounds with large levels of substitution to react successfully. Interestingly these reactions were also high yielding (80-97%) and the tri-substituted reaction only gave a single product. The tri-substituted allene **212** however, took longer to go to completion than the *di-substituted* example **211** (16 hours compared to 8 hours). The other allene gave a mixture of products indicting that the process was not very selective between the methyl and pentyl groups. There was a small level of selectivity toward placing the larger pentyl group further away from the carbonyl centre but this distinction was minimal (1: 1.25). In both reactions no products from addition of the carbonyl to the central carbon of the allene were observed. Given these positive results it was decided explore what levels of selectivity could be achieved with the *di-substituted* allenes. To this end a series of allenes were synthesised following the methodology outlined in scheme 71 keeping a pentyl group on one end of the allene and with varying groups on the other end: H, Me, pentyl, *iso*-propyl and phenyl. The Me, pentyl and phenyl substituted allenes were all made from the pentyl acetate. The *iso*-propyl allene was prepared from the *iso*-propyl acetate and pentylmagnesium bromide. The mono-substituted allene was synthesised by a different route to the other allenes (scheme 76). All the allenes could be stored for several weeks at -20 °C with the exception the phenyl-pentyl allene. Even with storage at -20°C this allene requires purification prior to use.



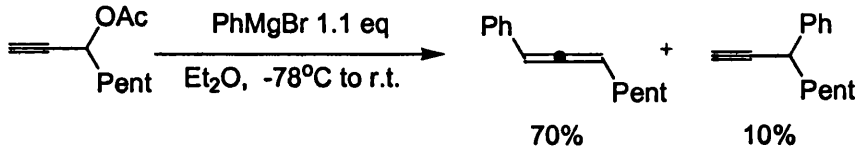
67%

215

Reaction carried out by RL Woodward

Scheme 76: Synthesis of mono-substituted allene

The synthesis of the phenyl substituted allene proved to have a particular problem in that during the synthesis a by-product is also formed presumably from substitution of the acetate group by the Grignard reagent (scheme 77).

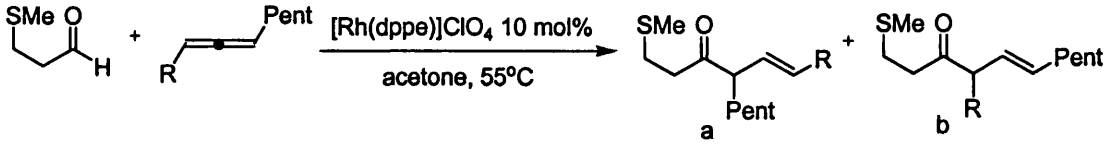


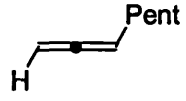
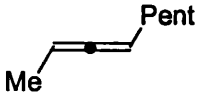
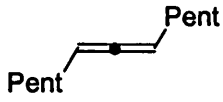
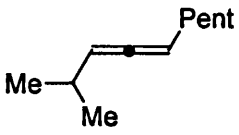
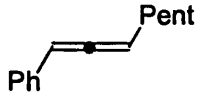
70% 10%

206 **216** **217**

Scheme 77: Synthesis of Phenyl allenes

This impurity is very hard to separate from the allene required, so very careful purification was needed. Although this impurity if present is at low levels, as it is an alkyne and hence highly reactive it can seriously lower the yields of the desired product if any is present. The equivalent by-product was not observed in any of the di-alkyl allenes synthesised.

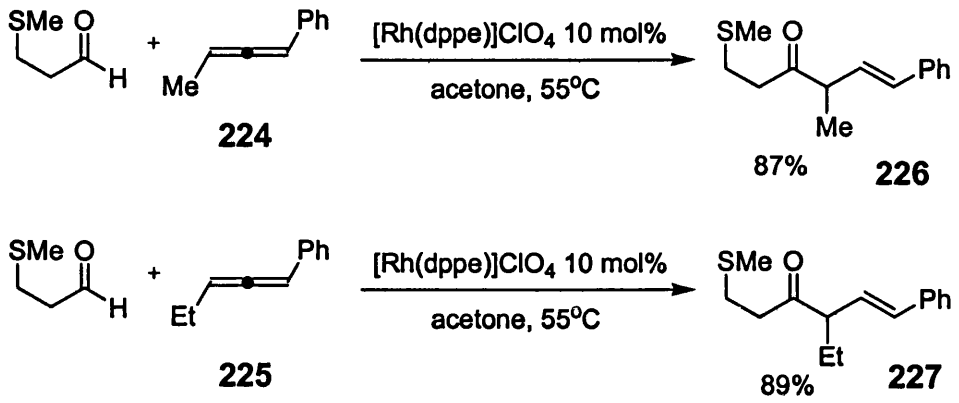


entry	allene	yield of allene synthesis (%)	time (h)	product	yield of hydroacylation[a,c] (%)	ratio of a:b[b]
1	 **215**	67	8	**220**	87	<1:20
2	 **211**	52	8	**213**	97	1:1.25
3	 **218**	70	8	**221**	70	n/a
4	 **219**	73	8	**222**	92	15:1
5	 **216**	75	8	**223**	89	>20:1

[a]Reactions carried out with 10 mol% [Rh(dppe)(NBD)}ClO_4 at 55 °C, [b]Determined by ^1H NMR, [c] isolated yields

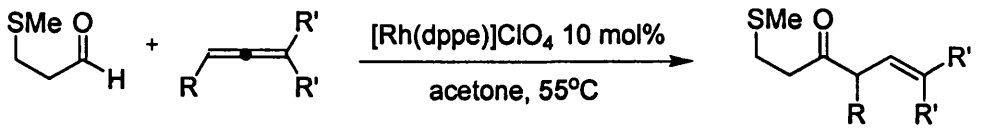
Table 41: Selectivity of allenes in the hydroacylation reaction

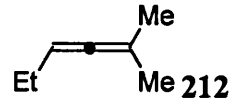
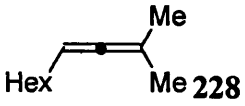
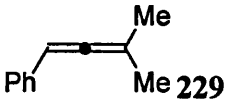
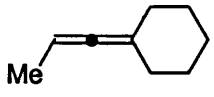
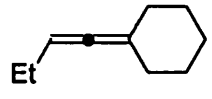
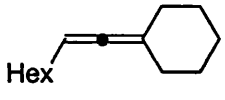
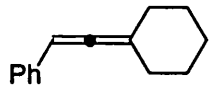
As can be seen the regio-selectivity of the reaction appears to be controlled by sterics. Where there is little difference in size of the allene substituents (entry 2, table 42) low selectivity levels are achieved. However, moving to larger differences in size (entries 4 and 5, table 42) complete regioselectivity is observed. To see if this is also the case with other substrates the methyl- and ethyl-phenyl allenes were synthesised and both also showed complete selectivity for placing the carbonyl group adjacent to the aliphatic moiety.



Scheme 78: Reactivity of Ph substituted allenes

The reactivity of the tri-substituted allenes was also investigated. The initial test (scheme 75) indicated that only one product is formed from these allenes but it was important to see if this would be true of all cases, particularly where a phenyl group was to be placed α to the carbonyl. It was also of interest to see if other tri-substituted allenes would be as effective.



Entry	allene	yield of synthesis of allene[b] (%)	time (h)	product	yield of hydroacylation reaction[ab] (%)
1	 **212**	50	16	**214**	80
2	 **228**	69	16	**234**	74
3	 **229**	67	16	**235**	69
4	 **230**	65	16	**236**	78
5	 **231**	71	16	**237**	81
6	 **232**	68	16	**238**	89
7	 **233**	72	16	**239**	62

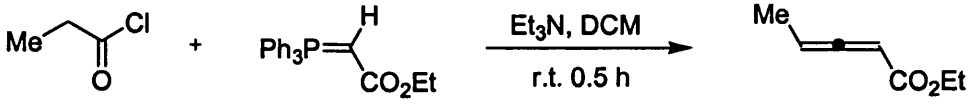
[a]Reactions carried out with 10 mol% [Rh(dppe)(NBD)]ClO_4 at 55 °C, [b]isolated yields

Table 42: Reactivity of tri-substituted allenes in the hydroacylation reaction

The results in table 42 show all the tri-substituted allenes give a single product even where the lone substituent is a bulky phenyl group. In each case there is complete selectivity for the less substituted end of the allene. The allenes themselves all had straightforward syntheses, although the examples substituted with ethyl and methyl groups were extremely volatile and so difficult to isolate. All the allenes needed to be stored at -20 °C. The products from the hydroacylation reactions were much more stable and were able to be stored at room temperature for several days.

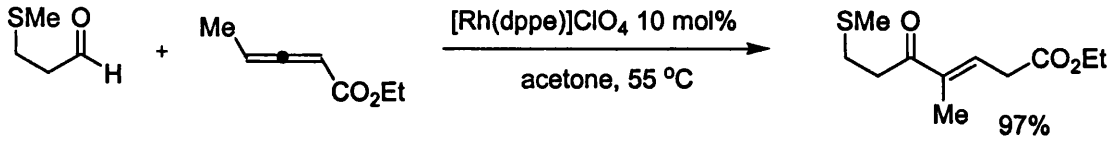
Until this point only allenes with alkyl or aromatic groups had been tested but we were keen to see the effect of an allene with an ester group. To this end allene **242** was synthesised following the procedure by Lang and Hansen using acid chlorides

and phosphoranylidene esters (Scheme 79).[141] It was decided to try a di-substituted allene to see if any regioselectivity could be observed.



240 241 242

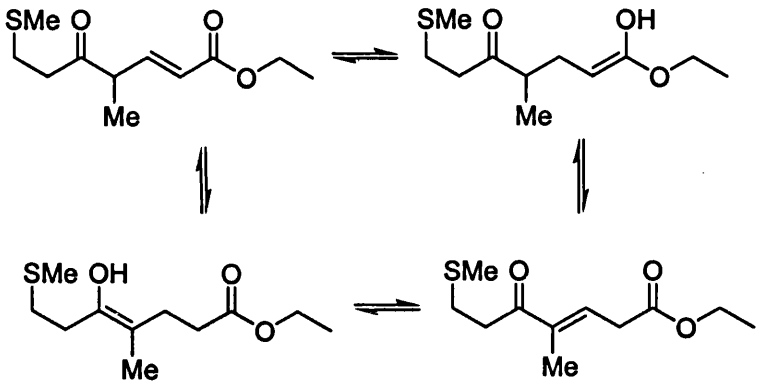
Scheme 79: Synthesis of allenic esters



242 243

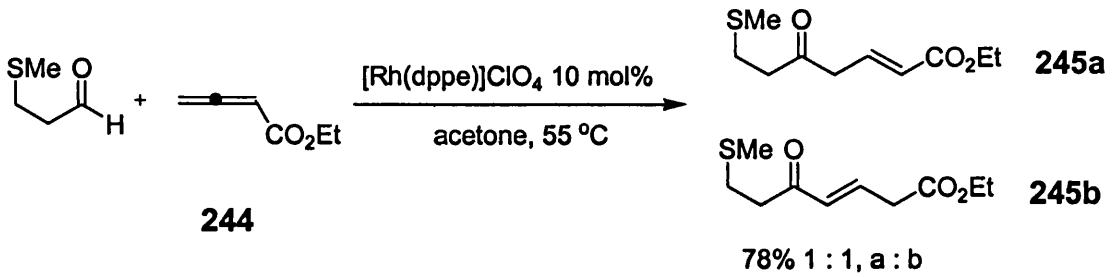
Scheme 80: Hydroacylation reaction with ethyl 2,3-pentadienoate

The ester substituted allene was reacted with our standard aldehyde (scheme 80). The product obtained at the end of hydroacylation reaction was not the expected compound. It appears that the system has complete regioselectivity, once again arguably due to the sterics involved, placing the ester group as far way from the aldehyde carbonyl as possible. However, it was apparent that a double bond migration had occurred under the reaction conditions to yield the conjugated enone product in excellent yield. Due to the potential for conjugation within the system the proton α to the carbonyl group is highly acidic, far more so than in the purely alkyl allene systems. It is therefore reasonable to assume the compound passes through the many possible tautomers (scheme 81), which ultimately leads to the conjugated enone product observed as the most thermodynamically stable compound.



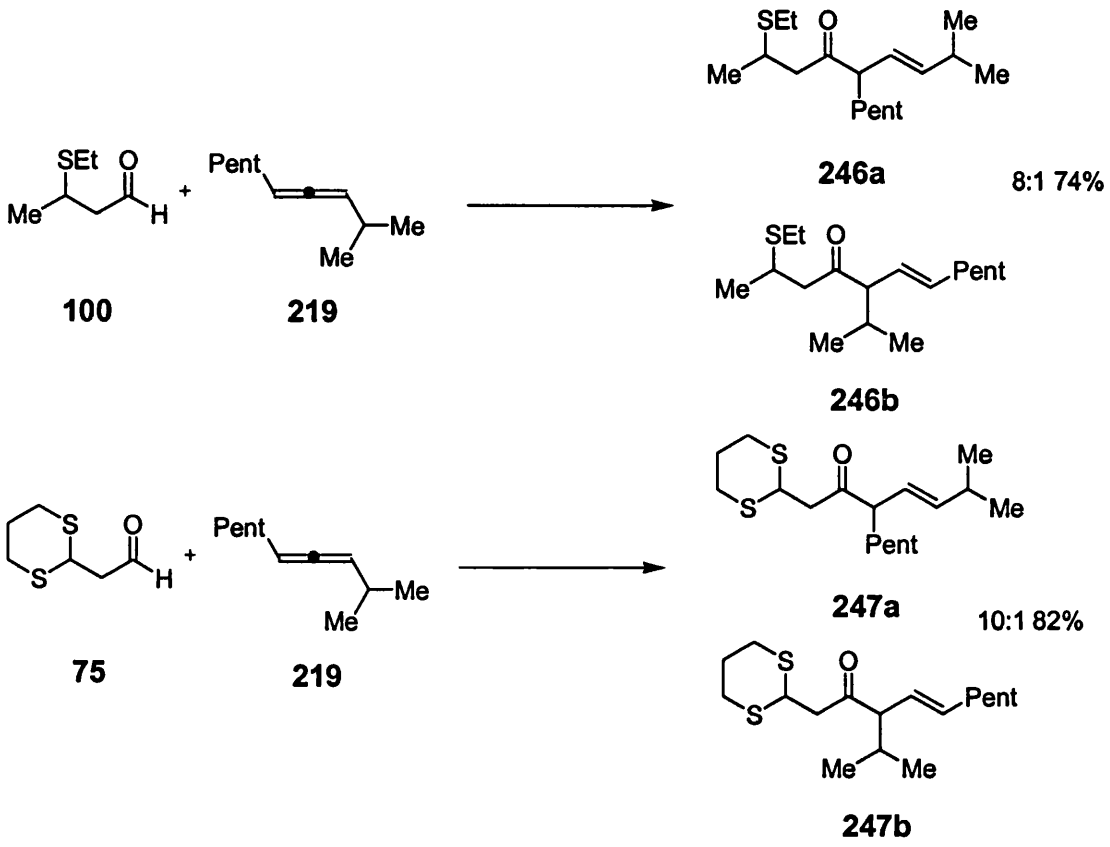
Scheme 81: Possible tautomers of 243

To investigate this further the monosubstituted allene **244** was synthesised and tried in the hydroacylation to see if this effect would be repeated. Again some isomerisation was observed however, in this case a 1:1 mixture of the isomerised and direct hydroacylation product was observed. This is not unexpected as while the proton adjacent to the ketone group is still far more acidic than the equivalent protons in the purely alkyl allenes the different in thermodynamic stability between the two structures (**245a** and **245b**) is not great.



Scheme 82: Reaction of ethyl buta-2,3-dienoate

To complete this work we were keen to show that the allenes were as reactive with the other types of aldehyde used in our hydroacylation reactions. To that end a reaction was undertaken with a dithiane and substituted sulfide aldehyde. The pentyl-*iso*propyl allene was chosen to see what effects on selectivity the different groups had.



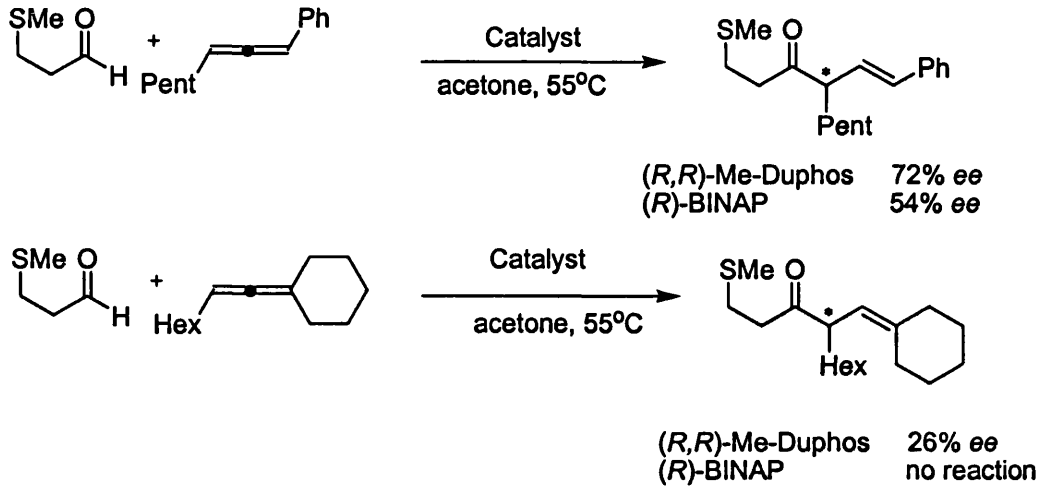
Scheme 83: Reaction of dithiane and substituted sulfide aldehydes

There were little differences in the selectivity's of these reactions. Both the dithiane and substituted sulfide aldehyde were less selective than methylthio propionaldehyde **61**. This loss in selectivity was not great however, the dithiane showing a ratio of 10:1 in favour of **247a** and the substituted sulfide a ratio of 8:1. These slight decreases perhaps indicate that the sterics of the aldehyde itself create some influence over the selectivity of the product obtained. Lack of time prevented any further study of this phenomenon but it would be interesting to look at this further in the future.

4.2 Intermolecular enantioselective hydroacylation reactions

Given the positive results obtained in the racemic reactions it was decided to try an enantioselective example to see if any selectivity could be achieved. Following the work done by Bosnich on enantioselective intramolecular hydroacylation reactions two catalysts were prepared that he had reported to be the most successful.[41] These were [Rh((*R*)-BINAP)]ClO_4 and [Rh((*R,R*)-Me-Duphos)]ClO_4.

As with the dppe catalyst these new catalysts were made as NBD precursors and activated directly before used with hydrogen immediately before reaction. For an initial test system two allenes were tried in the reaction, one of these was a tri-substituted allene and the other a di-substituted allene (scheme 84). To simplify these test reactions the fully selective pentyl-phenyl allene was chosen for the *di*-substituted example.



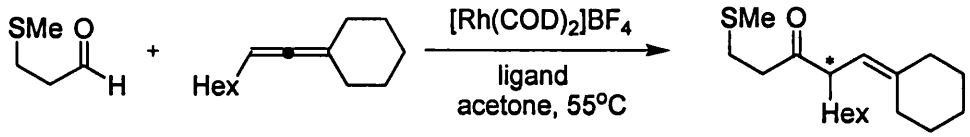
Scheme 84: Model systems for enantioselective hydroacylation reaction

As can be seem there was a dramatic difference between the two allenes. Although to our delight both reactions did give some degree of enantioselectivity, the tri-substituted example gave a low *ee* with the (*R,R*)-Me-Duphos catalyst (26%) and no reaction at all with BINAP. The pentyl-phenyl allene reacted with both catalysts and gave a very encouraging 72% *ee* with the (*R,R*)-Me-Duphos catalyst and a still promising, although lower, 54% *ee* with the (*R*)-BINAP catalyst. Reactions with both allenes and the new catalysts were slower than the previous reactions with the dppe catalyst. This may be the reason the tri-substituted allene, which has slower reaction time than the di-substituted examples, did not react with the BINAP catalyst. Given the large differences between these substrates it was decided to carry out investigations into both systems. One potential difference between the di- and tri-substituted allenes is that as allenes have chirality in their own right, it was not certain whether the di-substituted reaction was a kinetic resolution or a direct enantioselective reaction. In either case the reaction is interesting and as far as we are aware would be the first enantioselective intermolecular hydroacylation.

4.21 Tri-substituted allenes

The tri-substituted allenes were first investigated as although the initial results had a much lower *ee* there is no question about kinetic resolution, as these allenes are achiral.

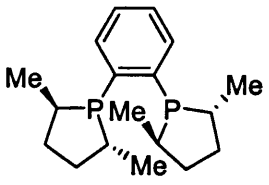
The logical starting point to improve the *ee* given the large differences in reactivity between the BINAP and Me-Duphos catalysts was to carry out a ligand screen. As reported in chapter 3 the *in-situ* catalyst generation would allow the easy screening of a wide range of ligands. Unfortunately this was not as easy with the allene reactions as had previously been the case with the alkene and alkyne systems. The allenes themselves seemed to be vulnerable from reaction to the silver salts present and none of the hydroacylation product could be obtained using this method. It was possible to generate the catalyst by first mixing the required substrates to form the catalyst (as before) and then filtering the resulting solution through a small syringe filter. This allowed the reaction to work with *ee*'s obtained for reactions carried out in this manner identical to those obtained for isolated catalysts indicating this is an adequate method for exploring the enantioselectivity of the reaction. These reactions did tend to require longer reaction times consistent with the previous findings of the catalyst investigations (chapter 3). A second catalyst generation was also discovered. The Undheim group using a similar catalyst system carried out hydroacylation experiments using $[Rh(COD)_2]BF_4$ and dppe.[21] In this process hydrogenation was still employed to displace the COD group. This should lead to the same active catalyst employed within our reactions. The system using $[Rh(COD)_2]BF_4$ and (*R,R*)-Me-Duphos was tried in the hydroacylation reaction with allenes and once again gave the same enantioselectivity and timing much closer to the pre-formed catalyst's. This catalyst system was used for the trial of different ligands due to its relative ease of use (Table 43).



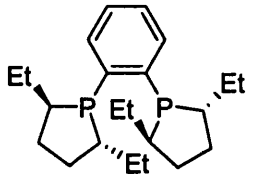
entry	ligand[a]	*ee* (%)[b]	yield (%)[c]
1	(*R,R*)-Me-Duphos	26	67
2	(*R,R*)-Et-Duphos	11	0
3	(*R,R*)-*i*Pr-Duphos	-	0
4	(*R,R*)-Me-BPE	15	65
5	(*S,S,R,R*)-Tangphos	8	20
6	(*R,R*)-DIPAMP	-	0
7	(*R*)-Chiraphos	36	70
8	(*R*)-Prophos	46	78
9	(*R,R*)-BDPP	31	68
10	(*R*)-BINAP	-	0
11	(*R*)-Tol-BINAP	-	0
12	(*R*)-TUNEPHOS	-	0
13	(*R*)-SpiroP	-	0

[a]Reactions carried out with 10 mol% $[Rh(COD)]BF_4$, 10 mol% ligand in acetone at 55 °C, [b]Determined by HPLC on a Chiracel AS-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 8.8 min; enantiomer 2 t_r = 9.8 min., [c] isolated yields

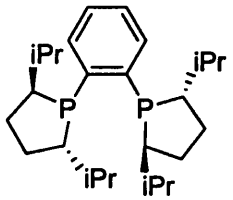
Table 43: Effect of ligands of the enantioselective intermolecular hydroacylation reaction with tri-substituted allenes



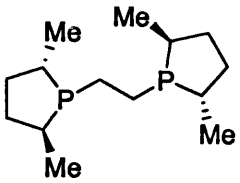
(*R,R*)-Me-Duphos
29



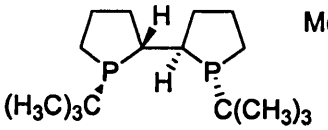
(*R,R*)-Et-Duphos
248



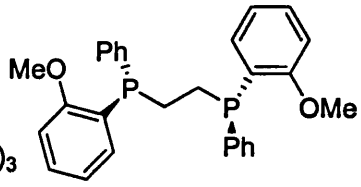
(*R,R*)-*i*Pr-Duphos
249



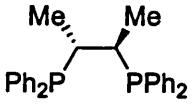
(*R,R*)-Me-BPE
250



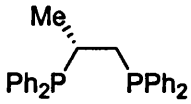
(*S,S,R,R*)-TANGPHOS
251



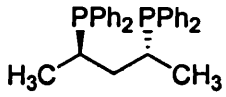
(*R,R*)-DIPAMP
252



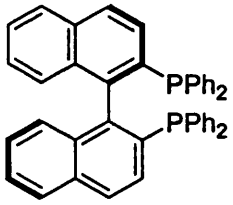
(*R,R*)-Chiraphos
30



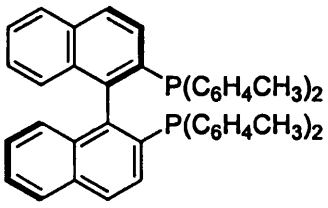
(*R*)-Prophos
253



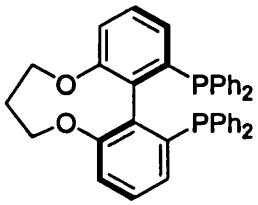
(*R,R*)-BDPP
254



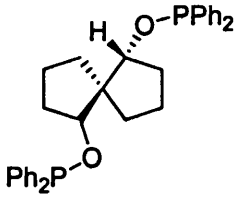
(*R*)-BINAP
28



(*R*)-Tol-BINAP
64



(*R*)-TUNEPHOS
255



(*R*)-SpiroP
256

Figure 14: Chiral ligands

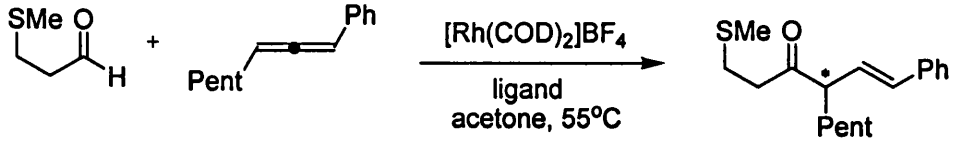
Unfortunately there were some problems with this ligand screen. The tri-substituted allenes are less reactive than the di-substituted examples and as a result many of the more bulky ligands did not give any reaction. This was not surprising given the result obtained with the BINAP catalyst in the initial reaction. The less sterically demanding ligands proved to be the more effective with these substrates although even the best

ligand found only gave a moderate level of enantioselectivity (46%). Me-Duphos proved to be among the best ligands for this system although only managing a 26 % *ee*. Chiraphos was slightly more selective delivering a 36% *ee*. Prophos was the best ligand found achieving a 46% *ee*. This level of selectivity is unfortunately very low however, and as a result of this and due to a lack of time no further work was attempted to improve this *ee*.

4.22 Di-substituted allenes

As the enantioselectivity achieved with the tri-substituted allenes was disappointing it was decided to move on to the di-substituted examples. As these are more reactive it was hoped a larger range of ligands would be successful in the reaction allowing an optimal system to be reached. With these substrates there was, however the question of whether the reaction was performing a kinetic resolution. This reaction is not a classical example of a kinetic resolution as although the allene will be the substance resolved the enantioselectivity of the product is the key feature. It was unclear whether the chiral nature of the allene would have a large effect on the enantioselectivities observed or if the catalyst itself would be the controlling factor. Equally in kinetic resolutions it is more usual for a diastereomeric product to be obtained in which the stereochemical nature of the substrate is in part retained. There are several examples of this type of resolution being carried out with allenes in the literature.[142-144]

It was decided to investigate the potential kinetic resolution with the most selective system possible as the more selective the reaction the greater the observable effects if a kinetic resolution is being carried out. For this reason a series of optimisation reactions were carried out with the aim of improving the *ee* of the product from the reaction before the question of kinetic resolution was explored. Firstly the ligand screen was repeated for these substrates. The phenyl-pentyl allene **216** was chosen as the test substrate due to the ease of separating the enantiomers of the products and of the allene itself.



entry	ligand[a]	*ee* (%)[b]	yield (%)[c]
1	(*R,R*)-Me-Duphos	71	71
2	(*R,R*)-Et-Duphos	34	60
3	(*R,R*)-*i*Pr-Duphos	30	62
4	(*R*)-BPE	26	70
5	(*R*)-Tangphos	60	67
6	(*R*)-DIPAMP	24	63
7	(*R*)-Chiraphos	32	68
8	(*R*)-Prophos	16	75
9	(*R,R*)-BDPP	20	72
10	(*R*)-BINAP	58	67
11	(*R*)-Tol-BINAP	-	0
12	(*R*)-TUNEPHOS	72	62
13	(*R*)-Spiro P	62	65

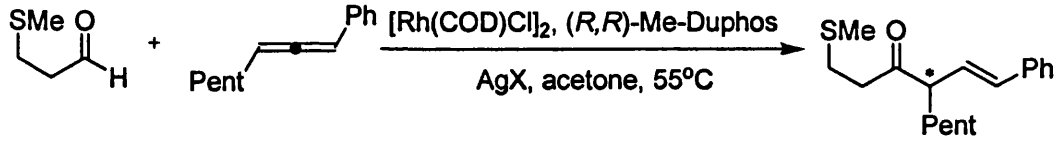
[a]Reactions carried out with 10 mol% $[Rh(COD)]BF_4$, 10 mol% ligand in acetone at 55 °C, [b]Determined by HPLC on a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min., [c] isolated yields

Table 44: Effect of ligands on the enantioselective intermolecular hydroacylation reaction with di-substituted allenes

To our pleasure a much larger range of ligands were successful in the reaction although again the more sterically demanding ligands gave slower reactions and in some cases incomplete conversion. It was still possible, however, to establish the enantioselectivity of the products obtained even in these cases. The best ligand found seemed to be the first one tried, (*R,R*)-Me-Duphos. Several other ligands gave rise to *ee*s similar to Me-Duphos with only (*R*)-TUNEPHOS performing slightly better in terms of *ee* but with a drop in yield. Interestingly Et-Duphos was significantly less selective than the Me-Duphos as was the *iPr*-Duphos. It was hoped that the larger groups on the ligand would give additional selectivity but this was not the case. Both these ligands along with the other more bulky ligands although successful in the

reaction took considerably longer to go to completion and the yields obtained were lower than with the less bulky ligands. As in the work performed on the catalyst system (chapter 3), ligands that were monodentate or hemilabile did not give rise to any product so the ligand search was restricted to *bis*-phosphines. Chiraphos, which gave good results for certain substrates for Bosnich, and related ligands which proved to be the best substrates in the tri-substituted allene screen gave very poor results for this system (30-40% *ee*).[41]

It was decided to try and see if any improvements could be made by using different counterions. For this it was necessary to use the *in-situ* catalyst generation procedure used for investigating catalyst improvements (chapter 3), filtering the catalyst solution before adding the substrates (table 45). These reactions were left for 36 hours after which time they had all gone to completion



entry	X[a]	*ee* (%)[b]
1	ClO_4	71
2	PF_6	69
3	BARF	55
4	BF_4	65
5	OTf	71
6	$[CB_{11}H_6Br_6]$	56

[a]Reactions carried out with 5 mol% $[Rh(COD)Cl]_2$, 10 mol% (*R,R*)-Me-Duphos, and 10 mol% AgX in acetone at 55 °C, [b]Determined by HPLC on a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min..

Table 45: Investigation of the effects of counterions on the *ee* of the intermolecular hydroacylation reaction.

As can be seen there are significant differences in the *ee* for different counterions. Once again it was found that the best counterion was the first one tried in the system; $AgClO_4$ (71% *ee*). The same *ee* was obtained with AgOTf while $AgBF_4$ gave a slightly lower level of selectivity. More interestingly the $[CB_{11}H_6Br_6]$ counterion

found to be the most successful at reducing reaction time in the catalyst study (chapter 3) gave a very poor *ee* (55%). Given these results it was decided to stay with $AgClO_4$ as the counterion of choice.

The search continued to investigate solvents and temperatures. Once again some small differences were observed. It was expected that lowering the reaction temperature would result in higher *ee* but previous work had indicated that the system is considerably less reactive at lower temperature. There was a concern therefore that reactions attempted at lower temperature would not work at all. This did become an issue with the lower temperatures, despite giving the best enantioselectivities, often resulting in extremely long reaction times and lower yields. The catalyst did not dissolve well in some solvents, e.g. DME, and for this reason solvent mixtures were employed to allow the reaction to proceed. The best solvent system found was a mixture of chloroform and acetone and this solvent mixture was tried at the lower temperature of 30 °C. This reaction was very successful with respect to the *ee* obtained but the yield and length of reaction were both poor.

entry	solvent (ratio)[a]	time (h)	temperature (°C)	conversion (%)[b]	*ee* (%)[c]
1	acetone	24	40	65	75
2	DCE	24	40	74	76
3	DME	48	40	10	81
4	DME/DCE	30	40	63	74
5	Dioxane/acetone	30	40	70	62
6	$CHCl_3$/acetone	30	40	68	82
7	Toluene/acetone	30	40	65	74
8	THF/acetone	30	40	64	71
9	$CHCl_3$/acetone	48	30	30	85

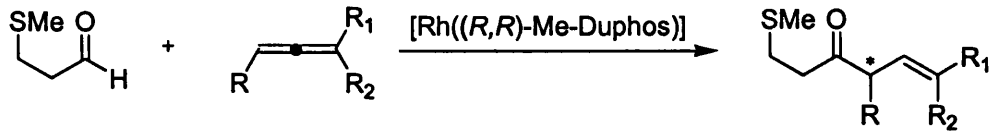
[a]Reactions carried out with 10 mol% [Rh(*R,R*)-Me-Duphos)]ClO_4,, [b]Determined by NMR, [c]HPLC on a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min..

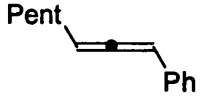
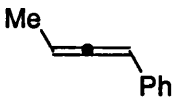
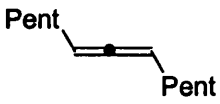
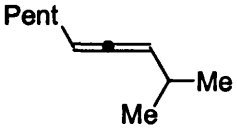
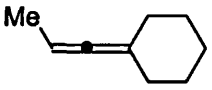
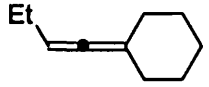
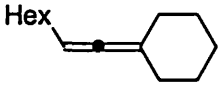
Table 46: Effect of solvent on enantioselectivities.

Other conditions were tried such as the use of additives including DMF, MeCN and molecular sieves. In particular, given the effect of MeCN when carrying out the work

on alkynes (chapter 2), it was hoped that the extra stabilisation effected by these additives may increase the selectivity of the reaction. Unfortunately exactly the same enantioselectivities were obtained from these reactions as those without any additives. The only effect bestowed by these additives appeared to be a lengthening of reaction time.

Once this optimisation work had been completed although the *ee* had not been improved to the levels hoped for it was decided to try all of the allene substrates so far prepared in the reaction to see how selective the reaction was overall. As the tri-substituted allene had shown some level of enantioselectivity with Me-Duphos (although not the most selective ligand for that substrate) and a range of these allenes were also tried in the enantioselective reaction. Unfortunately when the reactions were attempted at 30 °C only trace amounts of product were obtained ever after reaction for 72 hours so for this reason these experiments had to be carried out at 40 °C at which temperature they went to completion within 48 hours



entry	allene[a]	yield (%)[b]	*ee* (%)[c]
1		80	83
2		88	68
3		65	82
4		71	49
5		64	67
6		75	48
7		76	36

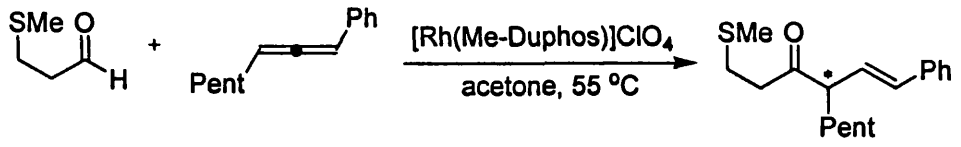
[a]Reactions carried out with 10 mol% [Rh(*R,R*)-Me-Duphos)]ClO_4, in 1:4 acetone: $CHCl_3$ at 40 °C, [b] isolated yields, [c]Determined by HPLC on a Chiracel OJ-H column or Chiracel AS-H column.

Table 47: Scope of enantioselective reactions

As can be seen in table 47 there was a mixture of success with these optimised reactions. The best enantioselectivity was obtained from the allene used to carry out the optimisation reactions with all the other allenes performing less well. Disappointingly the Me-Ph allene only gave rise to at 68% *ee* which may indicate that the Me group is too small to allow good selectivity between the two enantiomers. However, the best result in enantioselectivity of the tri-substituted allenes came from prop-1-enylidenecyclohexane (entry 5) although this was still only 67% *ee*. In this case it became apparent during the screening work on the tri-substituted allenes that the most reactive systems were the ones that lead to the highest enantioselectivities. Although this is only an observation it is possible that as prop-1-enylidenecyclohexane is the fastest reacting allene tried this is why the *ee* is greatest in this case. The pent-pent allene showed good selectivity virtually equivalent to the

Ph-Pent allene which is encouraging. However, the pent-*iso*propyl had a much lower 49% *ee* (entry 4 table 47) which is harder to explain. As this reaction is not completely selective it is possible that the choice between the two ends of the allene disrupts the enantioselectivity of the reaction. In the case of the Ph-pent allene the phenyl group may add some additional stabilisation or selectivity effects which may explain the high enantioselectivity. The pent-pent allene enantioselectivity may be explained by the fact that reaction can occur at either end of the allene with no loss of regioselectivity allowing the reaction to proceed quickly.

The optimised conditions in hand it was important to address the issue of whether a kinetic resolution of the allene was occurring. Firstly a series of experiments with different equivalents of allene (1, 2 and 5 with respect to aldehyde) were performed to see if any changes to the *ee* of the product or the remaining allene could be observed. These reactions were carried out at the higher temperature of 55 °C to try and force the reactions to go to completion to allow easy observation of any effects.



entry	time (h)	no. of allene equivalents	*ee* of allene (%)	amount of allene remaining[b]	*ee* of hydroacylation product (%)[c]	yield of hydroacylation product (%)[d]
1	24	1	26	0.35 eq	71	55
2	24	2	20	1.1 eq	71	67
3	24	5	9	4 eq	71	75

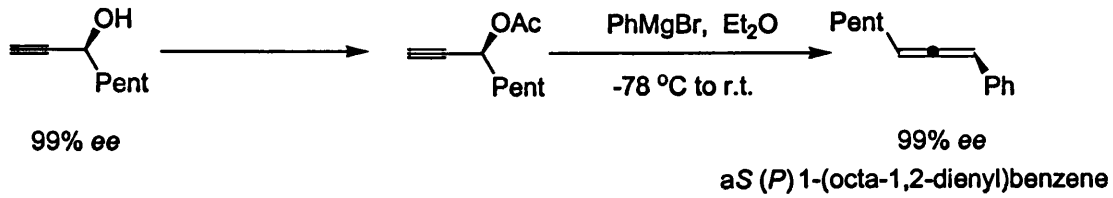
[a]Reactions carried out with 10 mol% [Rh(*R,R*)-Me-Duphos)]ClO_4, in acetone at 55 °C, [b] Determined by NMR spectroscopy [c]Determined by HPLC on a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min., [d] isolated yields

Table 48: Effect of number of equivalents of allene on enantioselectivity

Unfortunately, as can be seen these results were somewhat ambiguous with no definitive answer obtained. There is an increase in the *ee* of the allene which means that a kinetic resolution must be occurring. However, this increase is not very large perhaps indicating that the reaction is not very selective between the two enantiomers of allene. This observation may also suggest a second process is occurring that

reduced the *ee* of the remaining allene. Exactly the same *ee* is obtained from the product independent of the number of allene equivalents used. Given the yields of these different reactions were not the same this is not definitive. It may add credence however, to the possibility of a second process occurring in the reaction which reduced the *ee* of the remaining allene allowing more of the correct enantiomer of allene to become available for reaction. Another possibility is that although there is a kinetic resolution it is not highly selective and each enantiomer of allene leads to almost the same enantiomeric excess in the final product indicating the process is heavily catalyst controlled with respect to enantioselectivity.

The final experiments were carried out using a chiral allene. This was prepared using the same procedure that that used for the racemic allenes but employing an enantiopure alcohol to give the required product in 99% *ee* (scheme 85).[145]



Scheme 85: Synthesis of chiral allene

Both enantiomers of the catalyst were reacted with 0.75, 1 and 3 equivalents of the chiral allene (compared to aldehyde). All the reactions were tested in the best reaction conditions for *ee* found to make sure that the maximum effects would be seen (1:4 acetone:$CHCl_3$, 30 °C). For this reason the reactions were carried out over 36 hours to allow them to proceed as far as possible.

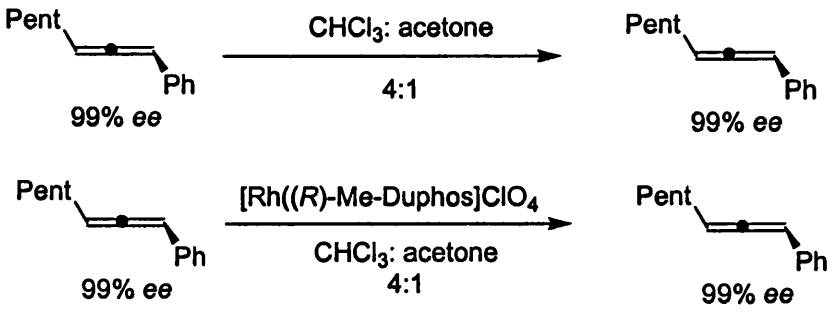
entry	catalyst[a]	equivalents of allene	conversion (%)[b]	*ee* of allene (%)[c]	*ee* of product (%)[d]
1	[Rh(*R,R*)-Me-Duphos]ClO_4	0.75	45	74	-59
2	[Rh(*R,R*)-Me-Duphos]ClO_4	1	65	76	-60
3	[Rh(*R,R*)-Me-Duphos]ClO_4	3	65	75	-61
4	[Rh(dppe)]ClO_4	3	100	90	59
5	[Rh(*S,S*)-Me-Duphos]ClO_4	0.75	60	73	83
6	[Rh(*S,S*)-Me-Duphos]ClO_4	1	70	74	85
7	[Rh(*S,S*)-Me-Duphos]ClO_4	3	75	76	82

[a]Reactions carried out with 10 mol% [Rh(R,R)-Me-Duphos)]ClO_4, in acetone at 30 °C, [b]Determined by NMR, [c]Determined by HPLC with a Chiracel OD-H column (hexane), 0.3 mL/min; enantiomer 1 t_r = 19.5 min; enantiomer 2 t_r = 22.8 min [d]Determined by HPLC on a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min..

Table 49: Reactions with enantiopure allene

The results obtained from these reactions were very surprising. There is an obvious matched and mis-matched system, again reinforcing the presence of a kinetic resolution occurring. The enantioselectivities from these two systems do not differ as significantly as would be expected. The matched system gives an 85% *ee* equivalent to the best enantioselectivities observed with the racemic reaction while the mis-matched system still gives a respectable 60% *ee* (entries 2 and 6, table 49). In these two cases the major enantiomer was different. One enantiomer was the major with the (*S,S*)-Me-Duphos and the other enantiomer became the more dominant with the (*R,R*)-Me-Duphos. The conversions of these two reactions were also slightly different. The matched (*S,S*)-Me-DuPhos system gave a 75% conversion (67% yield) while the (*R,R*)-Me-Duphos only gave a 65% conversion (61% yield). As the matched system gave the same *ee* as the reaction with an excess of the racemic allene this logically indicates that in the racemic reaction only one enantiomer must be reacting. However, this does not appear to be the only story as confusingly, when the enantiopurity of the allene itself was tested at the end of the reaction it became apparent that some racemisation had occurred. Despite starting with allene that had an *ee* of 99% at the end of the reaction with both the (*S,S*)-Me-Duphos and (*R,R*)-Me-Duphos catalysts the *ee* had fallen to 75%. Given that racemisation had occurred to an

extent it is not possible to say definitely that only one enantiomer had reacted with the (*S,S*)-Me-Duphos catalyst. This racemisation process may also explain why reactions with less than one equivalent of allene are capable of yielding products with the same *ee* as those with at least two equivalents. This may also be part of the reason such a relatively high *ee* is obtained from the reaction with the (*R,R*)-Me-Duphos catalyst (i.e the mis-matched system). Equally interesting is that this *ee* is largely the same with both catalysts, and for the different number of equivalents of allene used. This may indicate that the racemisation process is independent of the hydroacylation reaction as it may be expected that with the larger numbers of equivalents of allene the *ee* would be higher than with the lower levels of allene. However, given the long reaction times it is entirely possible that the allene would have racemised to the same extent in each case. To see if the racemisation is independent of the hydroacylation reaction two reactions were carried out. One with the allene just in the solvent used for the reaction (chloroform: acetone 4:1) and one with (*R,R*)-Me-Duphos catalyst in the same solvent both with the chiral allene. These reactions were then heated to 30 °C for the same length of time as that used for the original reactions.



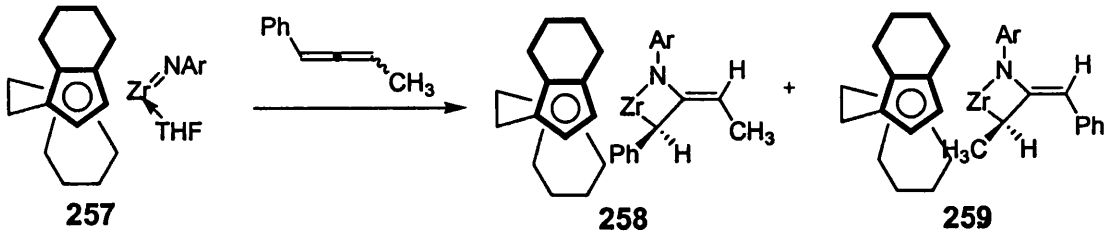
Scheme 86: Investigations into the racemisation of chiral allene

Thermal racemisation of chiral allenes is documented[146] and although relatively low temperatures were used for the reaction it is possible the additional effect of the rhodium source allows racemisation to occur. Both these test reactions showed no signs of racemisation indicating that the aldehyde is required for racemisation to occur. This appears to indicate some step in the hydroacylation reaction, or a rhodium species only formed in the presence of the aldehyde, may be responsible for the racemisation. All mechanistic studies performed for hydroacylation so far have indicated that each step in the catalytic cycle is reversible with the exception of the

final reductive elimination. Despite this it is unclear what mechanism could be responsible for this racemisation. Due to lack of time no further investigations were made to explore this reaction. Possibly deuterium labelling of the allene or aldehyde may give further insight into the mechanisms involved and this would be something to explore in the future.

The reaction carried out with the dppe catalyst showed a surprisingly high level of enantioselectivity of 61% *ee* (78% yield) indicating the chirality of the allene is able to transfer to the product to a reasonable extent. As this is not a direct comparison to the Me-Duphos catalyst, which could only be achieved by using a racemic Me-Duphos catalyst, it may not follow that the same level of enantioselectivity would be observed with this catalyst. Given the fairly high level of selectivity it is fair to assume that where no other influencing factors are present the chirality of the allene becomes predominant and is able to exercise a reasonable degree of control over the reaction. In this case the major enantiomer was the same as in the matched case (with (*S,S*)-Me-Duphos). Given this result it shows even more conclusively how much enantiocontrol comes from the catalyst as with the mis-matched system the opposite enantiomer is formed despite the natural preference of the allene.

These potentially unusual reactions with allenes are not unique. Other groups have also found enantioselective reactions that do not work as might be expected when using allenes. The Bergman group have reported reactions using a zirconocene imido complex **257** and 1,3-disubstituted allenes.[147, 148] A highly selective kinetic resolution occurs along with a stereoinversion of the allene involved. Using 1-phenyl-1,2-butadiene they found the products to be a 1:1 mixture of **258** and **259** (scheme 87).



257 **258** **259**

Scheme 87: Reaction of enantiopure zirconocene imido complex with racemic allene

Neither of the other possible products were observed indicating the reaction is highly diastereoselective, if not regioselective. When enantiopure zirconium complex **257** was used with excess racemic allene a highly selective kinetic resolution was observed. However when only one equivalent of the racemic allene was employed the product from the reaction was still the single diastereomer rather than the expected mixture of products. They rationalised this result by proposing that the slower reacting allene undergoes inversion of its absolute configuration when it reacts, allowing quantitative conversion to a single product. They proposed a stepwise mechanism consistent with these findings as although previous work had suggested organometalic cycloadditions proceed in a concerted manner there was no obvious way to explain these results assuming this condition. In a similar manner given the unusual nature of this reaction involving allenes it is possible the mechanism of the hydroacylation reaction with allenes has equivalent peculiarities that allow both the enantioselective nature of the products to be created along with the racemisation of enantiopure allene.

This work has demonstrated the possibility of performing enantioselective intermolecular hydroacylation reactions and is, as far as we are aware, the first report of such a reaction.

5 Conclusions and Future work

5.1 Conclusions

A large range of β-*S*-substituted aldehydes have been successfully reacted with a range of alkenes to yield with good regioselectivity the linear isomer. Additionally a wide range of alkynes have been employed with excellent selectivity for the *E*-linear isomer in good yield. A novel CN-directing effect has been observed and shown to be responsible for reversing the regioselectivity in a number of hydroacylation reactions. Catalyst loadings as low as 0.1 mol% were also achievable with the alkyne hydroacylation reactions.

A new catalyst system had been developed employing DPEphos as ligand allowing the additional use of 1-octene as a substrate in the hydroacylation reaction as well as removing the need for the use of hydrogen activation. This catalyst has also allowed the production of crystal structures proving the ability of the sulfur atom on 3-methylthio propionaldehyde to act as a chelate to the rhodium centre. Additionally the extra stability of the DPEphos ligand has been shown by the observation of the relatively stable rhodium-hydride species.

A range of allenes have been successfully employed in the hydroacylation reaction to give high yielding unconjugated enone products. The first enantioselective intermolecular hydroacylation reactions have been successfully carried out and have shown promise in the enantioselectivities achieved.

5.2 Future Work

Further study is needed to create a range of allenes with varying aryl groups to investigate the effect on the enantioselectivity observed. Additionally deuterium studies may allow the elucidation of the mechanism responsible for the racemisation of the chiral allene.

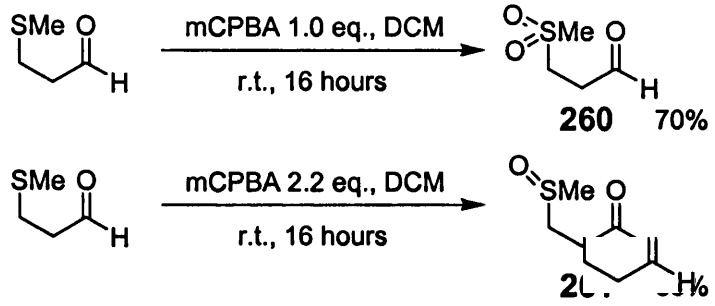
Different chelating groups would allow for a greater range of aldehyde substrates to be employed in the hydroacylation reaction. In particular oxygen and phosphorous groups are promising candidates for further investigation.

Further catalyst modification may allow the use of di, and tri-substituted alkenes which would allow an easier route of enantioselective products. This would also greatly extend the range of substrates the reaction is applicable to.

Given the highly successful nature of the alkyne hydroacylation reactions it may now be possible to manipulate the products of these reactions further allowing the formation of more synthetically useful substrates such as heterocycles.

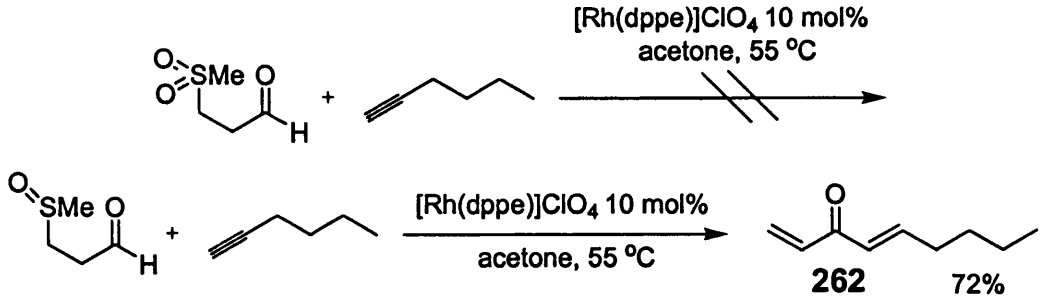
Appendix 1: Sulfoxide and sulfone aldehydes

Given the success of the sulfide aldehydes we were interested to see what reactivity would be gained from a sulfoxide and sulfone. For this reason the most reactive methyl sulfide aldehyde was oxidised to the corresponding sulfoxide and sulfone using mCPBA (scheme 88).[149]



Scheme 88: Synthesis of sulfoxide and sulfone aldehydes

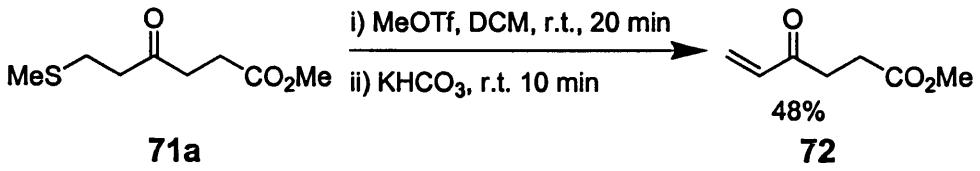
These aldehydes were then tried in the hydroacylation reaction with 1-hexyne as this is the most reactive unsaturated compound to date and therefore would be the most likely to show any reactivity (scheme 89).



Scheme 89: Hydroacylation reaction of sulfoxide and sulfone aldehydes

The sulfone did not show any reactivity despite prolonged reaction times (48 hours) and catalyst loadings (10 mol%). The sulfoxide however, did prove to be reactive in the system showing some unexpected side effects. The reaction was left for 48 hours before work-up to allow for any reaction to take place as the reaction is hard to monitor by TLC due to the highly polar nature of the aldehyde. After this time we were surprised to discover the product obtained from the reaction was hydroacylation product with the sulfoxide group eliminated in good yield (72%). Although

elimination of the sulfide group is known, this requires another reaction using MeOTf and base (scheme 89).



71a 72

Scheme 89 Removal of the –SMe group

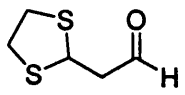
Sulfoxides are known to undergo elimination reactions when heated, particularly when adjacent to an electron withdrawing group. Given the group is in a β-position to the ketone and that relatively mild temperatures were used during the reaction, this effect is more unusual, although it is possible that the rhodium catalyst aids this decomposition in some way. This is an exciting development as it yields an easily functionalised compound, removing the sulfur group, without the need for a second reaction. It would be interesting to explore this reaction further to see if it is applicable to other substrates and to judge the time needed for the reaction to occur more accurately however, lack of time prevented this study.

Chapter 6 Experimental

General considerations

IR spectra were recorded using NaCl discs on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz, unless otherwise noted, using the residual solvent as an internal standard. *J* values are given in Hz. ^{13}C NMR spectra were obtained on a Bruker Avance 300 spectrometer at 75 MHz, unless otherwise noted using the residual solvent as an internal standard. ^{31}P NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 121 MHz. Mass spectrometry measurements were performed at the EPSRC National Spectrometry Service Centre, University of Wales Swansea. Elemental analyses were performed at the microanalysis service, University of Bath, using an Exeter Analytical Inc. CE-440 elemental analyser. Anhydrous acetonitrile, Et_2O, DCM, hexane, toluene and THF were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Dioxane, DCE and DME were distilled over calcium hydride and stored over 4 Å molecular sieves. DMF was distilled under reduced pressure over 4 Å molecular sieves and stored over Å molecular sieves. Acetone was distilled from Drierite and stored over 4Å molecular sieves. Petrol refers to the fraction of petroleum ether obtained between 40-60 °C. All glassware was dried in an oven and allowed to cool under nitrogen prior to use. All reactions were carried out under argon unless otherwise stated. All commercial reagents were used as obtained unless otherwise stated. Flash chromatography was conducted under medium pressure, using matrix 60 silica.

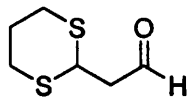
The general procedure for the reduction of ester compounds (A) as exemplified by [1,3]dithiolan-2-yl-acetaldehyde 74



DIBAL-H (1 M in DCM, 5.50 mL, 55 mmol) was added dropwise over 5 minutes to ester **77** (990 mg, 55 mmol) in DCM (30 mL) at –78 °C. The reaction was allowed to warm to room temperature over 2 hours. It was then quenched with a saturated

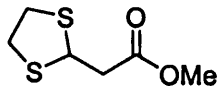
solution of Rochells salt (50 mL) and diluted with DCM (100 mL). The organic extracts were then washed with Rochelles salt (1 × 100 mL) and water (2 × 100mL). The combined aqueous extracts were extracted with DCM (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$) and reduced *in vacuo*. They were purified under flash chromatography (1:9 Et_2O: Petrol) to yield the title compound **75** as a yellow oil (0.68 g, 78%); δ_H (300 MHz; $CDCl_3$) 9.73 (1H, s, C*H*O), 4.83 (1H, t, *J* 6.7, S*CH*), 3.30-3.20 (4H, m, SCH_2CH_2S), 2.99 (2H, d, *J* 6.7, CH_2); δ_C (75 MHz; $CDCl_3$) 199.0, 52.3, 45.3, 38.4. Data consistent to that reported in the literature.[110]

Preparation of [1,3]dithian-2-yl-acetaldehyde 75



The general procedure for the reduction of ester compounds (**78**) was followed employing: Ester **78** (520 mg, 2.5 mmol), DIBAL-H (1 M in DCM, 2.55 mL, 2.5 mmol) and DCM (20 mL). Flash chromatography gave the title compound **76** as a yellow oil (280 mg, 70% yield); δ_H (300 MHz; $CDCl_3$) 9.72 (1H, t, *J* 1.8 *CH*O), 4.49 (1H, t, *J* 6.9, S*CH*), 2.98-2.78 (6H, m, including 2H, dd, *J* 6.9, 1.8, S$CH_2CH_2CH_2$S and CHCH_2), 2.16-2.06 and 1.94-1.79 (2H, m, $SCH_2CH_2CH_2S$); δ_C (75 MHz; $CDCl_3$) 199.0, 52.3, 45.3, 39.5, 38.4. Data consistent to that reported in the literature.[110]

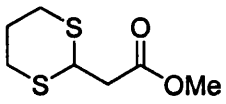
General procedure (B) for the preparation of thioacetal compounds as exemplified by [1,3]dithiolan-2-yl-acetic acid methyl ester 76



Ethane dithiol (0.83 mL, 11.6mmol) was added to methyl propriolate (1.0 mL, 10.5 mmol) in MeOH (16 mL) and DCM (4 mL) at –10 °C. NaOMe (0.7 g, 13mmol) was then added and the resulting solution stirred at –10 °C overnight and warmed to room temperature in the morning. It was then quenched with NH_4Cl (20 mL) and the product extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and water (20 mL) and dried ($MgSO_4$). It was then reduced *in vacuo* and purified with flash chromatography (1: 9 Et_2O: Petrol) to yield

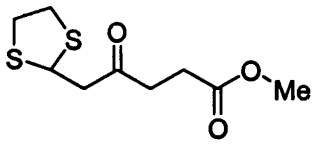
the title compound **77** as a colourless oil (1.50 g, 85% yield); δ_H (300 MHz; $CDCl_3$) 4.78 (1H, t, *J* 7.4, *CH*) 3.65 (3H, s, O*Me*), 3.22-3.16 (4H, m, SCH_2CH_2S), 2.80 (2H, d, *J* 7.4 CHCH_2); δ_C (75 MHz; $CDCl_3$) 170.4, 51.3, 47.2, 44.2, 38.0. Data consistent to that reported in the literature.[150]

Preparation of [1,3]dithian-2-yl-acetic acid methyl ester 77



General procedure (**B**) for the preparation of thioacetal compounds was followed employing: Ethyl proprioate (2.00 mL, 19.6 mmol), MeOH (32 mL), DCM (8 mL), propane dithiol (2.18 mL, 21.6 mmol) and NaOMe (1.40 g, 25.5 mmol). Flash chromatography gave the title compound **78** as a pale yellow oil (3.52 g, 87% yield); δ_H (300 MHz; $CDCl_3$) 4.32 (1H, t, *J* 7.4, *CH*), 3.63 (3H, s, O*Me*), 2.83-2.79 (4H, m, S$CH_2CH_2CH_2$S), 2.70 (2H, d, *J* 7.4, CHCH_2CO), 2.07-1.97 and 1.87-1.74 (2H, m, $SCH_2CH_2CH_2S$); δ_C (75 MHz; $CDCl_3$) 169.4, 51.4, 41.1, 39.7, 28.8, 24.5. Data consistent to that reported in the literature.[151]

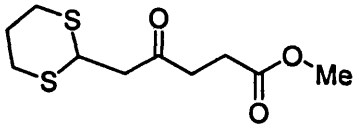
The general procedure for the hydroacylation reaction (C) as exemplified by 5-[1,3]dithiolan-2-yl-4-oxo-pentanoic acid methyl ester 78



Acetone (2.5 mL) was added under argon to pre-catalyst [Rh(nbd)(dppe)]ClO_4 (9 mg, 0.027 mmol). The catalyst was activated *in situ* by bubbling though the solution with H_2 for 2 minutes untill a colour change from orange to yellow was observed. After this time the solution was purged with argon. To this solution methyl acrylate (121 μL, 1.35 mmol) was added followed by aldehyde **74** (40 mg, 0.27 mmol). The resulting mixture was stirred and heated at 55 °C for 2 hours. After this time the solution was reduced *in vacuo* and purified by flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **78** as a yellow oil (44 mg, 70%); ν_{max} (film) /cm^{-1} 2970, 1720, 1665, 1421, 1265, 765; δ_H (300 MHz; $CDCl_3$) 4.83 (1H, br. s, *CH*), 3.67 (3H, s, O*Me*), 3.22 (4H, br. s, SCH_2CH_2S), 3.04 (2H, d, *J* 7.0, CHCH_2), 2.72 (2H, d, *J* 6.4, CO$CH_2CH_2CO_2$Me), 2.61 (2H, t, *J* 6.4, $COCH_2CH_2CO_2$Me); δ_C

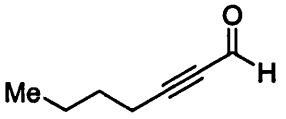
(75 MHz; $CDCl_3$) 206.4, 173.4, 53.0, 52.3, 47.1, 38.9, 37.8, 27.9; *m/z* (ES) 235 (20%, $[M]^+$), 105 (10%, $[M\text{-}CH_2COCH_2CH_2CO_2Me]^+$); found $[M+NH_4]^+$ 252.0723, $C_9H_{18}NO_3S_2$ requires 252.0728.[112]

Preparation of 5-[1,3]dithian-2-yl-4-oxo-pentanoic acid methyl ester 79



The general procedure for the hydroacylation reaction (**C**) was followed employing: Pre-catalyst $[Rh(nbd)(dppe)]ClO_4$ (13 mg, 0.02 mmol), acetone (2 mL), aldehyde **75** (30 mg, 0.2 mmol) and methyl acrylate (121 μL, 1.35 mmol). Heated at 55 °C for 2 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **79** as a yellow oil (32 mg, 74%); ν_{max} (film) /cm^{-1} 3055, 2979, 1735, 1720, 1438, 1265, 909 738; δ_H (300 MHz; $CDCl_3$) 4.50 (1H, t, *J* 7.0, *CH*), 3.67 (3H, s, O*Me*), 2.94-2.75 (8H, m, $SCH_2CH_2CH_2S$ and $CHCH_2COCH_2$), 2.62 (2H, t, *J* 6.5, $COCH_2CH_2CO_2Me$), 2.17-2.06 and 1.93-1.79 (2H, m, $SCH_2CH_2CH_2S$); δ_C (75 MHz; $CDCl_3$) 203.3, 172.0, 50.9, 46.8, 40.1, 37.0, 29.2, 26.6, 24.2; *m/z* (EI) 248 (40%, $[M]^+$), 161 (40%, $[M\text{-}C_2H_4CO_2Me]^+$); found $[M]^+$ 248.0535, $C_{10}H_{16}O_3S_2$ required 248.0535.[112]

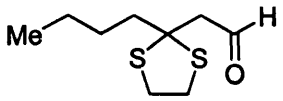
The general procedure for the preparation of aldehyde compounds (D) as exemplified by hept-2-ynal 80



To 1-Hexyne (1.50 mL, 18.2 mmol) in THF (50 mL) at –78 °C, *n*-BuLi 2.5M (7.30 mL, 18.2 mmol) was added dropwise. The resulting solution was stirred at –78 °C for 1 hour and then LiBr (1.91 g, 22 mmol) was added followed by DMF (7.07 mL, 91 mmol) added dropwise over 10 minutes. The reaction was stirred at –78 °C for 30 minutes and then raised to 0 °C overnight. The reaction was quenched with saturate NH_4Cl (aq) (30 mL) and extracted with Et_2O (3 × 30 mL). The combined orgainic extracts were washed with brine (30 mL) and water (30 mL), dried ($MgSO_4$) and reduced *in vacu*. Flash chromatography (1:9 Et_2O: Petrol) yielded the title compund **80** as a colourless oil (1.52 g, 76% yield); δ_H (300 MHz; $CDCl_3$) 9.15 (1H, s, *CH*O),

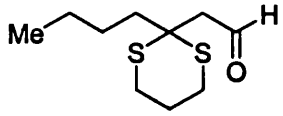
2.40 (2H, t, *J* 6.9, CC*CH*$_2$), 1.57 (2H, tt, *J* 7.1, 6.9, CCCH$_2$*CH*$_2$), 1.41 (2H, tq, *J* 7.1, 6.6 CCCH$_2$CH$_2$*CH*$_2$), 0.83 (3H, t, *J* 6.6, CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 177.4, 98.3, 84.2, 29.8, 25.2, 18.5, 16.0. Data consistent to that reported in the literature.[152]

Preparation of (2-pentyl-[1,3]dithiolan-2-yl)-acetaldehyde 21



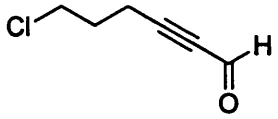
General procedure (**B**) for the preparation of thioacetal compounds was followed employing: aldehyde 80 (100 mg, 0.9 mmol), MeOH (8 mL), DCM (2 mL), 1,3-propanedithiol (0.08 mL, 1.0 mmol) and NaOMe (70 mg, 1.1 mmol). Flash chromatography (1:9 EtOAc: Petrol) yielded the title compound **81** (0.14 g, 76%) as a yellow oil; δ_H (300 MHz; $CDCl_3$) 9.73 (1H, t, *J* 2.4 *CH*O), 3.27 (4H, br. s, SC*H*$_2$*CH*$_2$S), 2.85 (2H, d, *J* 2.4, CHOC*H*$_2$), 1.93-1.88 (2H, m, CC*H*$_2$CH$_2$), 1.44-1.21 (4H, m CCH$_2$*CH*$_2$*CH*$_2$CH$_3$), 0.89 (3H, t, *J* 7.2, CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 199.0, 81.9, 39.7, 38.5, 30.0, 23.6, 23.3, 14.0. Data consistent to that reported in the literature.[101]

Preparation of (2-pentyl-[1,3]dithian-2-yl)-acetaldehyde 82



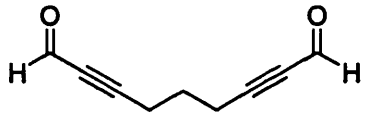
The general procedure for the preparation of thioacetal compounds (**B**) was followed employing: Aldehyde **80** (210 mg, 1.8 mmol), 1,3-propanedithiol (0.2 mL, 1.9 mmol), MeOH (16 mL), DCM (4 mL) and NaOMe (130 mg, 2.0 mmol). Flash chromatography (1:9 EtOAc: Petrol) yielded the title compound **82** (0.31 g, 78% yield) as a yellow oil; δ_H (300 MHz; $CDCl_3$) 9.71 (1H, td, *J* 2.8, 0.9 *CH*O), 2.89-2.72 (6H, m, SC*H*$_2$CH$_2$*CH*$_2$S and *CH*$_2$CHO), 2.03-1.82 (4H, m, CC*H*$_2$*CH*$_2$CH$_2$CH$_3$), 1.49-1.39 (2H, m, *CH*$_2$CH$_3$), 1.34-1.22 (2H, m SCH$_2$*CH*$_2$CH$_2$S), 0.87 (3H, t, *J* 7.2, CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 200.2, 50.5, 49.7, 40.6, 26.6, 26.5, 25.1, 23.2, 14.3. Data consistent to that reported in the literature.[101]

Preparation of 6-chloro-hex-2-ynal 84



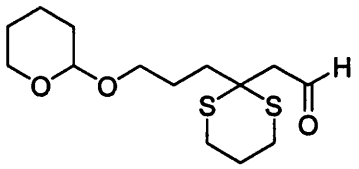
The general procedure for the preparation of aldehyde compounds (**D**) was followed employing; 5-chloro-1-pentyne (1.00 g, 9.7 mmol), THF (100 mL), *n*-BuLi 2.5M (3.90 mL, 9.7 mmol), LiBr (1.00 g, 11 mmol) and DMF (3.8 mL, 49 mmol). Flash chromatography (1:4 EtOAc:Petrol) gave the title compound **84** as a yellow oil (0.89 g, 71% yield); ν_{max} (film)/cm^{-1} 2966, 1683, 893, 723; δ_H (300 MHz; $CDCl_3$) 9.17 (1H, t, *J* 0.8, *CHO*), 3.65 (2H, t, *J* 6.1, Cl*CH*$_2$), 2.63 (2H, td, *J* 6.9, 0.8, CCCH$_2$), 2.05 (2H, tt, *J* 6.9 6.1, CH$_2$*CH*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 177.1, 96.7, 82.2, 43.3, 30.4, 16.7; *m/z* (EI) 130 (40%, $[M]^+$), 89 (30% $[M\text{-}CHOC]^+$), 54 (40% $[M\text{-}ClCHOC]^+$); found $[M\text{-}H]^+$ 129.0102, C_6H_6ClO requires 129.0100.[112]

Preparation of nona-2,7-diynedial 85



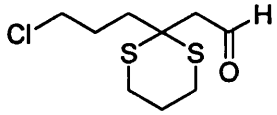
The general procedure for the preparation of aldehyde compounds (**D**) was followed employing: *n*-BuLi 2.5M (3.44 mL, 8 mmol), 1,6-heptadiyne (400 mg, 4 mmol) , THF (50 mL), LiBr (900 mg, 10 mmol) and DMF (3.3 mL, 40 mmol). Flash chromatography (1:4 EtOAc:Petrol) gave the title compound **85** as a colourless oil (0.50 g, 80% yield); ν_{max} (film)/cm^{-1} 2968, 1735, 1373, 1240, 1101; δ_H (300 MHz; $CDCl_3$) 9.12 (2H, t, *J* 0.7, 2 × *CHO*), 2.52 (4H, td, *J* 7.0 0.7, 2 × CC*CH*$_2$), 1.85 (2H, tt, J 7.0, 7.0, CH$_2$*CH*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 177.2, 96.7, 82.7, 25.9, 18.5; *m/z* (EI) 148 (1%, $[M]^+$), 119 (70% $[M\text{-}CHO]^+$), 91 (100% $[M\text{-}CHOCHO]^+$). Acc mass not possible due to high breakdown of sample.[112]

Preparation of {2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-[1,3]dithian-2-yl}-acetaldehyde 87



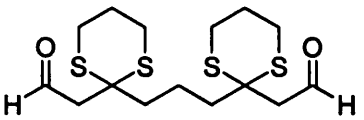
The general procedure for the preparation of thioacetal compounds (**B**) was followed employing aldehyde **83**[153] (200 mg, 1.0 mmol), 1,3-propanedithiol (0.11 mL, 12 mmol), MeOH (8 mL), DCM (2 mL) and NaOMe (100 mg, 18 mmol). Flash chromatography (1:9 EtOAc: Petrol) gave the title compound **87** (0.19 g, 63%) as a yellow oil; ν_{max} (film)/cm^{-1} 3044, 2372, 1642, 1406, 1267, 734; δ_H (300 MHz; $CDCl_3$) 9.75 (1H, t, *J* 2.8, *CH*O), 4.54 (1H, t, *J* 4.1, *CH* pyran), 3.84-3.68 (2H, m, OCH_2 pyran), 3.50-3.35 (2H, m, OCH_2CH_2), 2.85-2.81 (6H, m, $SCH_2CH_2CH_2S$ and CH_2COH) 2.12-2.06 (2H, m, $OCHCH_2$) 2.00-1.89 (2H, m, CCH_2) 1.83-1.74 (4H, m, $SCH_2CH_2CH_2S$ and $CHCH_2$ pyran) 1.57-1.45 (4H, m, $OCH_2CH_2CH_2$ pyran); δ_C (75 MHz; $CDCl_3$) 198.9, 98.1, 66.2, 61.7, 49.6, 48.5, 36.3, 30.1, 25.5, 24.8, 24.04, 23.96, 19.0; *m/z* (EI) 304 (90%, $[M]^+$), 220 (60% $[M\text{-}OCH_2CH_2CH_2CH_2C]^+$), 85 (60% $[M\text{-}CHOCH_2CS_2C_3H_6C_3H_6O]^+$); found $[M+NH_4]^+$ 322.1505, $C_{14}H_{28}NO_3S_2$ requires 322.1503.[112]

Preparation of [2-(3-chloro-propyl)-[1,3]dithiane-2-yl]-acetaldehyde 88



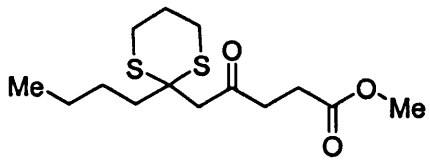
The general procedure for the preparation of thioacetal compounds (**B**) was followed employing 6-chloro-hex-2-ynal **84** (1.07 g, 8.2 mmol), 1,3-propanedithiol (0.9 mL, 9.0 mmol), MeOH (64 mL), DCM (16 mL) and NaOMe (580 mg, 10.7 mmol). Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **88** as a yellow oil (1.23 g, 63%); ν_{max} (film) /cm^{-1} 2987, 1739, 1373, 1240, 1047; δ_H (300 MHz; $CDCl_3$) 9.69 (1H, t, *J* 2.8, *CH*O), 3.49 (2H, t, *J* 6.2, $ClCH_2$), 2.81-2.75 (6H, m, $SCH_2CH_2CH_2S$ and CH_2CHO), 2.70 (2H, t, *J* 6.1, $ClCH_2CH_2CH_2$), 2.09 (2H, tt, *J* 6.2 6.1, $ClCH_2CH_2CH_2$), 2.02-1.97 and 1.82-1.77 (2H, m, $SCH_2CH_2CH_2S$); δ_C (75 MHz; $CDCl_3$) 199.7, 50.8, 49.2, 45.1, 37.8, 27.9, 26.5, 24.8; *m/z* (EI) 238 (40% $[M]^+$), 195 (20% $[M\text{-}CHOCH_2]^+$); Acc mass not possible due to high rate of compound breakdown.[112]

Preparation of (2-{3-[2-(2-oxo-ethyl)-[1,3]dithiane-2-yl]-propyl}-[1,3]dithiane-2-yl)-acetaldehyde 89



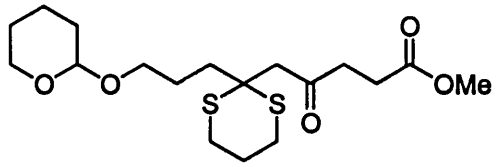
The general procedure for the preparation of thioacetal compounds (**B**) was followed employing 1,3-propanedithiol (0.2 mL, 1.8 mmol), NaOMe (120 mg, 2.2 mmol), aldehyde **85** (130 mg, 0.8 mmol), MeOH (16 mL) and DCM (4 mL) at –10 °C. Flash chromatography (1:1, EtOAc:Petrol) yielded the title compound **89** as a yellow oil (0.23 g, 80%); ν_{max} (film)/cm^{-1} 2942, 2248, 1714, 908, 734; δ_H (300 MHz; $CDCl_3$) 9.73 (2H, t, *J* 2.8, 2 × *CH*O), 2.84-2.78 (12H, m, 2 × S*CH*$_2$CH$_2$*CH*$_2$S and 2 × *CH*$_2$CHO), 1.99-1.94 (8H, m, C*CH*$_2$CH$_2$*CH*$_2$C and 2 × SCH$_2$*CH*$_2$CH$_2$S), 1.78-1.69 (2H, m, CCH$_2$*CH*$_2$CH$_2$C); δ_C (75 MHz; $CDCl_3$) 198.5, 59.4, 49.4, 48.2, 39.2, 25.3, 18.4; *m/z* (EI) 364 (50%, $[M]^+$), 229 (100% $[M\text{-}M\text{-}HCOSCH_2CH_2CH_2S]^+$), 175 (75% $[M\text{-}HCOCH_2CSCH_2CH_2CH_2SCH_2CH_2]^+$); found $[M+H]^+$ 365.0732, $C_{15}H_{25}O_2S_4$ requires 365.0740.[112]

Preparation of 5-(2-butyl-[1,3]dithian-2-yl)-4-oxo-pentanoic acid methyl ester 91



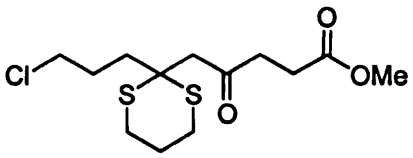
The general procedure for the hydroacylation reaction (**C**) was followed employing: Pre-catalyst $[Rh(nbd)(dppe)]ClO_4$ (9 mg, 0.027 mmol), acetone (2 mL), Aldehyde **82** (20 mg, 0.27 mmol) and methyl acrylate (121 μL, 1.35 mmol). Heated at 55 °C for 18 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **91** as a yellow oil (190 mg, 63%); ν_{max} (film)/cm^{-1} 3054, 2986, 1693, 1669, 1422, 1265, 735; δ_H (300 MHz; $CDCl_3$) 3.68 (3H, s, O*Me*), 3.12 (2H, s, SCC*H*$_2$CO), 2.99-2.76 (6H, m, SC*H*$_2$CH$_2$C*H*$_2$S and COC*H*$_2$CH$_2$CO), 2.59 (2H, t, *J* 6.3, COCH$_2$C*H*$_2$CO), 2.12-1.86 (4H, m, SCH$_2$C*H*$_2$CH$_2$S and SCC*H*$_2$CH$_2$), 1.55-1.43 (2H, m, SCCH$_2$C*H*$_2$CH$_2$), 1.41-1.28 (2H, m, C*H*$_2$CH$_3$), 0.93 (3H, t, *J* 7.2, CH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 205.1, 173.5, 52.1, 50.6, 49.6, 39.9, 39.0, 28.1, 26.8, 26.6, 25.4, 23.1, 14.3; *m/z* (EI) 322 (100%, $[M+NH_4]^+$), 175 (90%, $[M\text{-}COCH_2CH_2CO_2Me]^+$); found $[M+NH_4]^+$ 322.1505, $C_{14}H_{28}NO_3S_2$ requires 322.1505.[112]

Preparation of 4-oxo-5-{2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-[1,3]dithiane-2-yl}-pentanoic acid methyl ester 92



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(nbd)(dppe)]ClO_4 (5 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **87** (40 mg, 0.13 mmol) and methyl acrylate (60 μL, 0.68 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **92** as a yellow oil (32 mg, 60%); ν_{max} (film) /cm^{-1} 2960, 2940, 1717, 1684, 1456, 1367, 1100, 765; δ_H (300 MHz; $CDCl_3$) 4.53 (1H, t, *J* 3.4, O*CH*CH_2), 3.83-3.65 (2H, m, O*CH*$_2$$CH_2$), 3.61 (3H, s, O*Me*), 3.47-3.32 (2H, m, O*CH*$_2$ furan), 3.04-3.02 (2H, m, C*CH*$_2$CO), 2.81 (2H, t, *J* 7.7, SCH_2CH_2*CH*$_2$S), 2.80 (2H, t, *J* 6.6, CO*CH*$_2$$CH_2CO_2Me$), 2.52 (2H, t, *J* 6.6, $COCH_2$*CH*$_2$$CO_2Me$), 2.13-2.07 (2H, m, S*CH*$_2$$CH_2CH_2S$), 2.01-1.86 (2H, m, OCH*CH*$_2$ furan), 1.80-1.60 (4H, m, SCH_2*CH*$_2$$CH_2S$ and OCH_2CH_2*CH*$_2$), 1.52-1.45 (6H, m, OCH_2*CH*$_2$*CH*$_2$ furan and OCH_2*CH*$_2$); δ_C (75 MHz; $CDCl_3$) 205.1, 173.5, 99.0, 62.6, 52.2, 50.5, 46.9, 43.9, 40.0, 35.8, 31.1, 28.1, 28.0, 26.8, 25.3, 25.1, 20.0; *m/z* (EI) 390 (40%, $[M]^+$), 289 (100% $[M\text{-}OCH_2CH_2CH_2CH_2COH]^+$), 275 (90% $[M\text{-}MeOCOCH_2CH_2CO]^+$); found $[M+NH_4]^+$ 408.1873, $C_{18}H_{34}NO_5S_2$ requires 408.1877.[112]

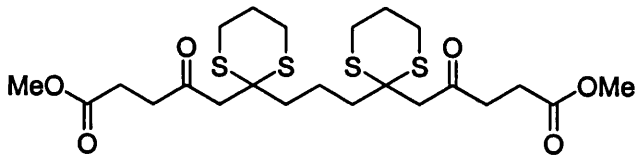
Preparation of 5-[2-(3-chloro-propyl)-[1,3]dithiane-2-yl]-4-oxo-pentanoic methyl ester 93



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(nbd)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (2.5 mL), aldehyde **88** (36 mg, 0.15 mmol) and methyl acrylate (70 μL, 0.75 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **93** as a yellow oil (34 mg, 71%); ν_{max} (film) /cm^{-1} 2346, 1750, 1740, 1647, 1231, 1041, 908; δ_H (300 MHz; $CDCl_3$) 3.61 (3H, s, O*Me*), 3.57 (2H, t, *J* 6.4. *CH*$_2$Cl), 3.06 (2H, s, C*CH*$_2$CO), 2.90-2.84 (6H, m, S*CH*$_2$$CH_2$*CH*$_2$S and CO*CH*$_2$$CH_2CO_2Me$), 2.59 (2H, t,

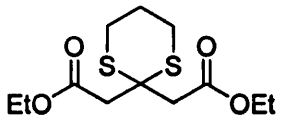
J 6.6, $COCH_2CH_2CO_2Me$), 2.26-2.20 (2H, m, $SCH_2CH_2CH_2S$), 2.06-1.96 (4H, m, $ClCH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 205.2, 173.5, 52.3, 50.1, 50.0, 45.3, 40.1, 36.2, 28.2, 28.1, 26.8, 25.2; *m/z* (EI) 342 (100%, $[M+NH_4]^+$), 289 (100%, $[M-Cl]^+$); found $[M+NH_4]^+$ 342.0959, $C_{13}H_{25}ClNO_3S_2$ requires 342.0961.[112]

Preparation of 5-(2-{3-[2-(4-methoxycarbonyl-2-oxo-butyl)-[1,3]dithiane-2-yl]-propyl}-[1,3]dithiane-2-yl)-4-oxo-pentanoic acid methyl ester 94



The general procedure for hydroacylation reaction (C) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (20 mg, 0.03 mmol), acetone (2.5 mL), aldehyde **89** (55 mg, 0.15 mmol) and methyl acrylate (67 μL, 0.75 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **94** as a yellow oil (67 mg, 84%); ν_{max} (film) /cm^{-1} 3105, 1735, 1720, 1570, 1422, 1265, 735; δ_H (300 MHz; $CDCl_3$) 3.60 (6H, s, 2 × O*Me*), 3.02 (4H, s, 2 × CCH_2CO), 2.82-2.78 (12H, m, 2 × $SCH_2CH_2CH_2S$ and 2 × $COCH_2CH_2CO2Me$), 2.52 (4H, t, *J* 6.5, 2 × $CH_2COCH_2CH_2CO_2Me$), 2.08-1.98 (4H, m, 2 × $SCH_2CH_2CH_2S$) 1.93-1.88 (4H, m, $CCH_2CH_2CH_2C$) 1.18 (2H, t, *J* 7.0, $CCH_2CH_2CH_2C$); δ_C (75 MHz; $CDCl_3$) 205.1, 173.6, 52.2, 50.7, 50.0, 47.3, 40.0, 38.9, 28.2, 26.8, 25.3; *m/z* (EI) 536 (30%, $[M]^+$), 429 (40% $[M-SCH_2CH_2CH_2SH]^+$), 315 (100% $[M-SCH_2CH_2CH_2SCOCH_2CH_2CO_2Me]^+$), 115 (90 % M-$C_{18}H_{29}O_3S_4$); found $[M+NH_4]^+$ 554.1733, $C_{23}H_{40}NO_6S_4$ requires 554.1728.[112]

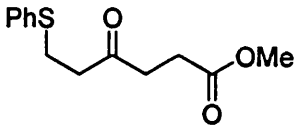
Preparation of 2-ethoxycarbonylmethyl[1,3]-dithian-2-yl-acetic acid ethyl ester 95



To diethyl 1,3-acetonedicarboxylate (1 mL, 4.4 mmol) in DCM (50 mL) at 0 °C was added propane-1,3-dithiol (0.44 mL, 4.4 mmol) and BF_3.OEt (0.93 g, 6.6 mmol). The resulting solution was stirred at 0 °C for 2 hours and then warmed to room

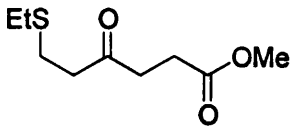
temperature. The reactino was quenched with sodium bicarbonate (aq) (30 mL) and extracted with DCM (3 × 20 mL) dried ($MgSO_4$) and reduced *in vacuo*. Flash chromatography (1:4 EtOAc: Petrol) yielded the title compound **95** as a pale yellow oil (0.97 g, 76%). δ_H (300 MHz; $CDCl_3$) 4.06 (4H, q, *J* 7.2, 2 × $CO_2CH_2CH_3$), 3.20 (4H, s, 2 × $COCH_2C$), 2.81 (4H, t, *J* 5.7, $SCH_2CH_2CH_2$), 1.93-1.86 (2H, m, $SCH_2CH_2CH_2S$), 1.17 (6H, t, *J* 7.2, 2 × OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 169.4, 61.0, 47.1, 42.7, 26.8, 24.8, 14.5; *m/z* (EI+) 292 (8%, $[M]^+$), 205 (40% $[M\text{-}CH_2CO_2Et]^+$), 45 (100% $[M\text{-}COCH_2SCH_2CH_2CH_2SCH_2COCH_2]^+$); found $[M+H]^+$ 293.0870, $C_{12}H_{21}O_4S_2$ requires 298.0876.[112]

Preparation of methyl 4-oxo-6-phenylthio-hexanoate 103



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)dppe]ClO_4$ (10 mg, 0.014 mmol), 3-(phenylsulfanyl)propionaldehyde (23 mg, 0.14 mmol) and methyl acrylate (65 μL, 62 mg, 0.70 mmol). Heated at 55 °C for 5 hours to give the title compound **103** as a colourless oil (33 mg, 92%); δ_H(300 MHz, $CDCl_3$) 7.30-7.08 (5H, m, Ar), 3.59 (3H, s, O*Me*), 3.59 (2H, *J* 7.2, $PhSCH_2CH_2$), 2.71 (2H, t, *J* 7.2, $PhSCH_2CH_2$), 2.67-2.60 (2H, m, $COCH_2CH_2CO_2Me$) 2.55-2.48 (2H, m, $COCH_2CH_2CO_2Me$); δ_C(75 MHz, $CDCl_3$) 207.5, 173.6, 52.3, 43.2, 37.7, 28.0, 26.6, 25.7, 15.1; *m/z* (EI) 252 (100%, $[M]^+$), 165 (20% $[M\text{-}CH_2CH_2CO_2Me]^+$), 137 (35% $[M\text{-}CO\ CH_2CH_2CO_2Me]^+$); found 252.0816 $[M]^+$ $C_{13}H_{16}O_3S$ requires 252.0816. Data consistent with literature.[154]

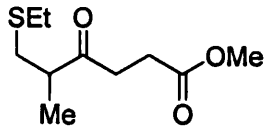
Preparation of methyl 6-ethylthio-4-oxo-hexanoate 104



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)dppe]ClO_4$ (10 mg, 0.014 mmol), 3-

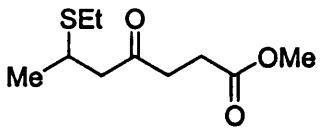
(ethylsulfanyl)propionaldehyde (17 mg, 0.14 mmol) and methyl acrylate (65 μL, 62 mg, 0.70 mmol). Heated at 55 °C for 1 hour to give the title compound **104** as a colourless oil (20 mg, 68%); δ_H(300 MHz, $CDCl_3$) 3.61 (3H, s, O*Me*), 2.71-2.65 (6H, m, EtS*CH*$_2$*CH*$_2$CO*CH*$_2$), 2.59-2.51 (2H, m, COCH$_2$*CH*$_2$CO$_2$Me), 2.48 (2H, q, *J* 7.3, CH$_3$*CH*$_2$S), 1.19 (3H, t, *J* 7.3, *CH*$_3$CH$_2$S); δ_C(75 MHz, $CDCl_3$) 207.5, 173.6, 52.3, 43.2, 37.7, 28.0, 26.6, 25.7, 15.1; ν_{max} (film)/cm^{-1} 2927, 1737, 1719, 1438; *m/z* (EI) 204 (15%, $[M]^+$), 143 (50% $[M\text{-EtS}]^+$), 111 (80% $[M\text{-EtSHOMe}]^+$); found 204.0814 $[M]^+$ $C_9H_{16}O_3S$ requires 204.0815.[116]

Preparation of 6-ethylthio-5-methyl-4-oxo-hexanoic acid methyl ester 105



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (7 mg, 0.010 mmol), acetone (2 mL), 3-ethylsulfanyl-2-methyl-propionaldehyde (26 μL, 0.2 mmol) and methyl acrylate (70 μL, 0.6 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **105** as a yellow oil (36 mg, 83%); ν_{max} (film)/cm^{-1} 3045, 2977, 1742, 1427, 1264, 753; δ_H (300 MHz; $CDCl_3$) 3.61 (3H, s, OCH_3), 2.86-2.64 (4H, m, CO*CH*$_2$*CH*$_2$), 2.57-2.43 (5H, m, S*CH*$_2$CH$_3$ and S*CH*$_2$*CH*CH$_3$), 1.20-1.10 (6H, m, SCH$_2$*CH*$_3$ and SCH$_2$CH*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 210.7, 172.7, 51.3, 46.0, 36.0, 33.8, 27.1, 26.3, 16.1, 14.3; *m/z* (EI) 218 (5%, $[M]^+$), 157 (90%, $[M\text{-}H_2CO_2Me]^+$), 125 (100%, EtSHOMe); found $[M]^+$ 218.0971, $C_{10}H_{18}O_3S$ requires 218.0972.[116]

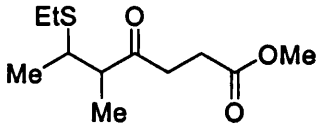
Preparation of 6-ethylthio-4-oxo-heptanoic acid methyl ester 106



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (9 mg, 0.013 mmol), acetone (2 mL), 3-

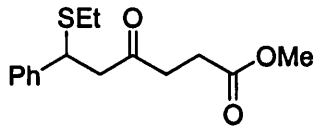
ethylsulfanyl-butyraldehyde (33 mg, 0.25 mmol) and methyl acrylate (112 μL, 0.75 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **106** as a yellow oil (42 mg, 77%); ν_{max} (film)/cm^{-1} 2950, 1736, 1652, 1556, 899, 731; δ_H (300 MHz; $CDCl_3$) 3.67 (3H, s, O*Me*), 3.34-3.22 (1H, m, CH_3CHSEt), 2.79-2.71 (4H, m, CH_2COCH_2), 2.62-2.52 (4H, m, $COCH_2CH_2$ and CH_3CH_2S), 1.28 (3H, d, *J* 6.8, CH_3CH), 1.24 (3H, t, *J* 7.4, CH_3CH_2S); δ_C (75 MHz; $CDCl_3$) 206.7, 173.0, 51.7, 50.0, 37.8, 34.6, 27.5, 24.5, 21.5, 14.6; *m/z* (EI) 218 (10%, $[M]^+$), 115 (90%, $[M\text{-}EtSMeCHCH_2]^+$) 89 (100% $[M\text{-}CH_2COCH_2CH_2CO_2Me]^+$); found $[M]^+$ 218.0968, $C_{10}H_{18}O_3S$ requires 218.0971.[116]

Preparation of methyl 6-ethylthio-5-methyl-4-oxo-heptanoate 107



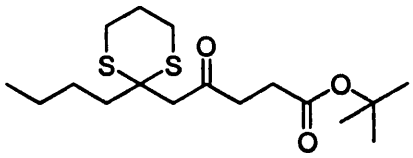
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)dppe]ClO_4$ (10 mg, 0.014 mmol), 3-(ethylsulfanyl)-2-methybutryaldehyde (20 mg, 0.14 mmol) and methyl acrylate (65 μL, 62 mg, 0.70 mmol). Heated at 55 °C for 20 hours to give the title compound **107** as a colourless oil (25 mg, 77%); δ_H(300 MHz, $CDCl_3$) (Major Diastereomer) 3.61 (3H, s, O*Me*), 3.07-2.92 (1H, m, CH_3CHSEt), 2.80-2.72 (2H, m, $COCH_2CH_2CO_2Me$), 2.61-2.42 (5H, m, $COCH_2CH_2CO_2Me$ and $CH_3CH_2SCHCH_3CH$), 1.24-1.14 (6H, m, $CH_3CH_2SCHCH_3CH$), 1.07 (3H, d, *J* 6.7, CH_3CHCO); (Minor Diasteromer) 3.61 (3H, s, OMe), 3.07-2.92 (1H, m, CH_3CHSEt), 2.80-2.72 (2H, m, $COCH_2CH_2CO_2Me$), 2.61-2.42 (5H, m, $COCH_2CH_2CO_2Me$ and $CH_3CH_2SCHCH_3CH$), 1.24-1.05 (9H, m, $CH_3CH_2SCHCH_3CHCH_3$); δ_C(75 MHz, $CDCl_3$) (both) 211.1, 210.8, 173.3, 173.3, 51.8, 51.7, 51.1, 42.3, 40.9, 37.1, 36.8, 31.9, 28.3, 27.62, 27.59, 25.3, 24.8, 20.3, 18.1, 14.8, 14.73, 14.68, 13.0; ν_{max} (film)/ cm^{-1} 2970, 2903, 1741, 1714, 1438; *m/z* (EI) 232 (5%, $[M]^+$), 171 (40% $[M\text{-}EtS]^+$), 115 (60% $[M\text{-}EtSCH(CH_3)CHCH_3]^+$); found 232.1129 $[M]^+$ $C_{11}H_{20}O_3S$ requires 232.1128.[116]

Preparation of 6-ethylthio-4-oxo-6-phenyl-hexanoic acid methyl ester 108



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (5 mg, 0.0075 mmol), acetone (2 mL), 3-ethylsulfanyl-3-phenyl-propionaldehyde (29 mg, 0.15 mmol) and methyl acrylate (67 μL, 0.45 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **108** as a yellow oil (37 mg 87%); ν_{max} (film) /cm^{-1} 3060, 1709, 1658, 1411, 1252, 903, 718; δ_H (300 MHz; $CDCl_3$) 7.29-7.12 (5H, m, Ar), 4.29 (1H, t, *J* 7.3, Ph*CH*), 3.56 (3H, s, O*Me*), 2.93 (2H, d, *J* 7.3, CH*CH_2*), 2.71-2.43 (4H, m, CO*CH_2CH_2*CO_2Me), 2.30-2.18 (2H, m, CH_3*CH_2*S), 1.08 (3H, t, *J* 7.4, *CH_3*CH_2S); δ_C (75 MHz; $CDCl_3$) 205.2, 172.5, 141.4, 128.1, 127.2, 126.8, 51.3, 48.8, 43.3, 37.5, 27.1, 24.9, 13.9; *m/z* (EI) 280 (10%, $[M]^+$), 115 (100%, $[M\text{-}EtSPhCHCH_2]^+$); found $[M]^+$ 280.1126, $C_{15}H_{20}O_3S$ requires 280.1128.[116]

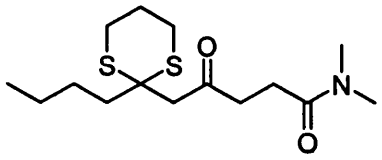
Preparation of 5-(2-Butyl-[1,3]dithiane-2-yl)-4-oxo-pentanoic acid tert-butyl ester 109



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and *tert*-butyl acrylate (95 μL, 0.65 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **109** as a yellow oil (33 mg, 70%); ν_{max} (film)/cm^{-1} 3003, 1740, 1647, 1427, 1334, 1180, 1026, 903; δ_H (300 MHz; $CDCl_3$) 3.05 (2H, s, C*CH_2*CO), 2.90-2.70 (6H, m, S*CH_2*CH_2*CH_2*S and CO*CH_2*CH_2CO_2*t*Bu), 2.43 (2H, t, *J* 6.6, $COCH_2$*CH_2*CO_2*t*Bu), 2.01-1.82 (4H, m, SCH_2*CH_2*CH_2S and *CH_2*$CH_2CH_2CH_3$), 1.51-1.43 (2H, m, CH_2*CH_2*CH_2CH_3), 1.37 (9H, s, CO_2*t*Bu), 1.30-1.23 (2H, m, CH_2CH_2*CH_2*CH_3), 0.85 (3H, t, *J* 7.2, $CH_2CH_2CH_2$*CH_3*); δ_C (75 MHz; $CDCl_3$) 205.4, 172.4, 81.0, 50.6, 49.7, 40.0, 39.1, 29.7, 28.5, 26.9, 26.7, 25.5, 23.2, 14.4; *m/z* (EI) 346 (10%, $[M]^+$), 233

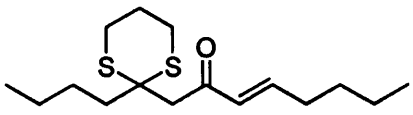
(20% [M-$CH_2CO_2{}^tBu$]$^+$), 189 (40% [M-$COCH_2CH_2CO_2{}^tBu$]$^+$), 175 (100%, [M-$CH_2COCH_2CH_2CO_2{}^tBu$]$^+$); found [M+H]$^+$ 247.1709, $C_{17}H_{11}O_3S_2$ requires 347.1708.[112]

Preparation of 5-(2-Butyl-[1,3]dithiane-2-yl)-4-oxo-pentanoic acid dimethylamide 110



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and dimethyl acrylamide (67 μL, 0.65 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **110** as a yellow oil (29 mg, 68%); ν_{max} (film)/cm^{-1} 2950, 2203, 1731, 1669, 1320, 970, 750; δ_H (300 MHz; $CDCl_3$) 3.13 (2H, s, CCH_2CO), 2.96 (3H, s, NCH_3CH_3), 2.94-2.96 (9H, m, NCH_3CH_3 and $SCH_2CH_2CH_2S$ and $COCH_2CH_2CONMe_2$), 2.54 (2H, t, *J* 6.4, $COCH_2CH_2CONMe_2$), 2.02-1.82 (4H, m, $SCH_2CH_2CH_2S$ and $CH_2CH_2CH_2CH_3$), 1.49-1.38 (2H, m, $CH_2CH_2CH_2CH_3$), 1.33-1.21 (2H, m, $CH_2CH_2CH_2CH_3$), 0.85 (3H, t, *J* 7.3, $CH_2CH_2CH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 206.7, 171.9, 50.7, 49.7, 40.2, 39.3, 37.5, 35.9, 27.8, 26.9, 26.5, 25.5, 23.2, 14.4; *m/z* (EI) 317 (20%, [M]$^+$), 217 (40% [M-$CH_2CH_2CONMe_2$]$^+$), 175 (100% [M-$CH_2COCH_2CH_2CONMe_2$]$^+$); found [M+H]$^+$ 318.1556, $C_{15}H_{28}NO_2S_2$ requires 318.1555.[112]

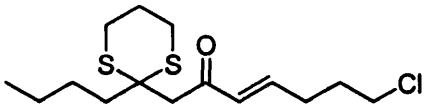
Preparation of (E)-1-(2-butyl-1,3-dithiane-2-yl)-oct-3-en-2-one 112



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and 1-hexyne (30 μL, 0.26 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **112** as a

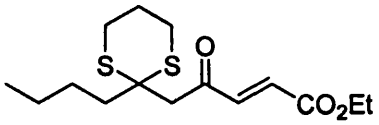
yellow oil (31 mg, 75%); ν_{max} (film)/cm^{-1} 2970, 1742, 1447, 1373, 1240, 1047; δ_H (300 MHz; $CDCl_3$) 6.80 (1H, dt, *J* 15.6, 6.9, $CCH_2COCHCH$), 6.12 (1H, dt, *J* 15.6, 1.5, CCH_2COCH), 3.06 (2H, s, CCH_2CO), 2.82-2.77 (4H, m, $SCH_2CH_2CH_2S$), 2.15 (2H, tdd, *J* 7.0, 6.9, 1.4, $COCHCHCH_2$), 2.05-1.85 (4H, m, $SCH_2CH_2CH_2S$ and $CCH_2CH_2CH_2CH_3$), 1.47-1.19 (8H m, $CCH_2CH_2CH_2CH_3$ and $CHCHCH_2CH_2CH_3$), 0.86 (3H, t, *J* 7.2, CH_2CH_3), 0.84 (3H, t, *J* 7.1, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 196.4, 148.3, 131.4, 51.6, 47.8, 38.9, 32.6, 30.6, 26.9, 25.5, 23.3, 22.7, 14.4, 14.2; *m/z* (EI) 300 (100%, $[M]^+$), 243 (80% $[M\text{-}CH_3CH_2CH_2CH_2]^+$), 225 (60% $[M\text{-}SCH_2CH_2CH_3]^+$); found $[M+H]^+$ 301.1654, $C_{16}H_{29}OS_2$ requires 301.1651.[112]

Preparation of (*E*)-1-(2-butyl-1,3-dithiane-2-yl)-7-chlorohept-3-en-2-one 113



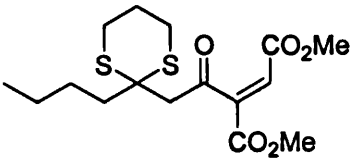
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and 5-chloro-1-pentyne (28 μL, 0.26 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4 EtOAc:Petrol) yielded the title compound **113** as a yellow oil (44 mg, 73%); ν_{max} (film)/cm^{-1} 2846, 2720, 1703, 1459, 1375, 719; δ_H (300 MHz; $CDCl_3$) 6.82 (1H, dt, *J* 15.6, 7.0, $CCH_2COCHCH$), 6.26 (1H, dt, *J* 15.6, 1.4, CCH_2COCH), 3.55 (2H, t, *J* 6.4, $CHCHCH_2CH_2CH_2Cl$), 3.13 (2H, s, CCH_2CO), 2.89-2.84 (4H, m, $SCH_2CH_2CH_2S$), 2.40 (2H, tdd, *J* 7.1, 7.0, 1.4, $COCHCHCH_2$), 2.10-1.91 (4H, m, $SCH_2CH_2CH_2S$ and $CCH_2CH_2CH_2CH_3$), 1.55-1.26 (4H, m, $CCH_2CH_2CH_2CH_3$), 0.93 (3H, t, *J* 7.3, $CCH_2CH_2CH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 195.3, 144.9, 131.5, 50.6, 47.5, 43.7, 38.2, 30.4, 29.1, 26.2, 24.7, 22.5, 13.7; *m/z* (EI) 320 (60%, $[M]^+$), 263 (100% $[M\text{-}CH_3CH_2CH_2CH_2]^+$), 245 (70% $[M\text{-}ClCH_2CH_2C]^+$), 213 (60% $[M\text{-}SCH_2CH_2CH_2S]^+$); found $[M+H]^+$ 321.1108, $C_{15}H_{26}ClOS_2$ requires 321.1113.[112]

Preparation of (*E*)-ethyl 5-(2-butyl-1,3-dithian-2-yl)-4-oxopent-2-enoate 114a and (*Z*)- ethyl 5-(2-butyl-1,3-dithian-2-yl)-4-oxopent-2-enoate 114b



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and ethyl propiolate (66 μL, 0.65 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compounds **114a** and **114b** as an inseperable mixture (4:1 E:Z) yellow oil (28 mg, 65%); ν_{max} (film)/cm^{-1} 2932, 1718, 1653, 1472, 1380, 910, 733; δ_H (300 MHz; $CDCl_3$) ((*E*)-ethyl 5-(2-butyl-1,3-dithian-2-yl)-4-oxopent-2-enoate **114a**) 7.18 (1H, d, *J* 15.8, $CCH_2CO\mathit{CH}$), 6.82 (1H, d, *J* 15.8, $CCH_2COCH\mathit{CH}$), 4.26 (2H, q, *J* 7.1, $CO_2\mathit{CH_2}CH_3$), 3.26 (2H, s, $C\mathit{CH_2}CO$), 2.97-2.77 (4H, m, $S\mathit{CH_2}CH_2\mathit{CH_2}S$), 2.11-1.91 (4H, m, $SCH_2\mathit{CH_2}CH_2S$ and $\mathit{CH_2}CH_2CH_2CH_3$), 1.43-1.23 (7H, m, $CO_2CH_2\mathit{CH_3}$ and $CH_2\mathit{CH_2}\mathit{CH_2}CH_3$), 0.93 (3H, t, *J* 7.3, $CH_2CH_2CH_2\mathit{CH_3}$); δ_C (75 MHz; $CDCl_3$) 195.9, 165.9, 140.3, 130.9, 61.8, 50.9, 48.9, 39.3, 30.1, 26.9, 25.3, 23.2, 14.5; ((*Z*)- ethyl 5-(2-butyl-1,3-dithian-2-yl)-4-oxopent-2-enoate **114b**) 6.65 (1H, d, *J*12.1, $CCH_2CO\mathit{CH}$), 5.97 (1H, d, *J* 12.1, $CCH_2COCH\mathit{CH}$), 4.44 (2H, q, *J* 7.1, $CO_2\mathit{CH_2}CH_3$) 3.41 (2H, s, $C\mathit{CH_2}CO$), 2.97-2.77 (4H, m, $S\mathit{CH_2}CH_2\mathit{CH_2}S$), 2.11-1.91 (4H, m, $SCH_2\mathit{CH_2}CH_2S$ and $\mathit{CH_2}CH_2CH_2CH_3$), 1.43-1.23 (7H, m, $CO_2CH_2\mathit{CH_3}$and $CH_2\mathit{CH_2}\mathit{CH_2}CH_3$), 0.93 (3H, t, *J* 7.3, $CH_2CH_2CH_2\mathit{CH_3}$); *m/z* (EI+) (both) 316 (20%, $[M]^+$), 189 (80% $[M\text{-}COCHCHCOOEt]^+$), 99 (100% $[M\text{-}CH_3(CH_2)_3\text{-}CS(CH_2)_3SCH_2CO]^+$); found $[M+H]^+$ 317.1240, $C_{15}H_{25}O_3S_2$ requires 317.1240.[112]

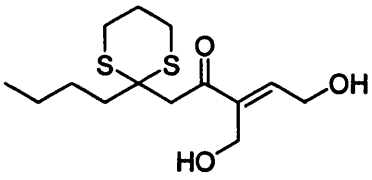
Preparation of dimethyl 2-(2-(2-butyl-1,3-dithian-2-yl)acetyl)maleate115



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and dimethyl acetylenedicarboxylate (32 μL, 0.26 mmol).

Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **115** as an inseperable mixture of isomers (3:1 Z:E) yellow oil (34 mg, 69%); ν_{max} (film)/cm^{-1} 2976, 1791, 1740, 1714, 1437, 1267; δ_H (300 MHz; $CDCl_3$) (major *Z*) 6.76 (1H, s, COC*CH*), 3.81 (3H, s, CO_2*Me*), 3.79 (3H, s, CO_2*Me*), 3.50 (2H, s, C*CH*$_2$CO), 2.95-2.72 (4H, m, S*CH*$_2$CH$_2$*CH*$_2$S), 2.19-2.13 (2H, m, *CH*$_2$CCH$_2$CO), 2.11-1.82 (2H, m, SCH$_2$*CH*$_2$CH$_2$S), 1.58-1.22 (4H, m, *CH*$_2$*CH*$_2$CH$_3$), 0.92 (3H, t, *J* 7.2, CH$_2$*CH*$_3$); (minor *E*) 6.70 (1H, s, COC*CH*), 3.89 (3H, s, CO_2*Me*), 3.79 (3H, s, CO_2*Me*), 3.30 (2H, s, C*CH*$_2$CO), 2.95-2.72 (2H, m, S*CH*$_2$CH$_2$CH$_2$S), 2.19-2.13 (2H, m, SCH$_2$CH$_2$*CH*$_2$S), 2.11-1.82 (4H, m, SCH$_2$*CH*$_2$CH$_2$S and *CH*$_2$CH$_2$CH$_2$CH$_3$), 1.58-1.22 (4H, m, CH$_2$*CH*$_2$*CH*$_2$CH$_3$), 0.92 (3H, t, *J* 7.2, CH$_2$CH$_2$CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) (*E* and *Z*) 197.1, 196.7, 165.3, 164.3, 164.2, 163.0, 146.1, 144.9, 128.1, 127.8, 52.8, 52.7, 52.4, 52.3, 50.2, 49.6, 49.3, 45.2, 38.2, 37.9, 26.2, 26.1, 26.0, 25.6, 24.8, 24.6, 22.6, 22.5, 13.7, 13.6; *m/z* (EI) 360 (30%, $[M]^+$), 254 (60% $[M\text{-}SCH_2CH_2CH_2S]^+$), 217 (100% $[M\text{-}CO_2MeCCHCO_2Me]^+$); found $[M+H]^+$ 360.4912, $C_{16}H_{25}O_5S_2$ requires 360.4908.[112]

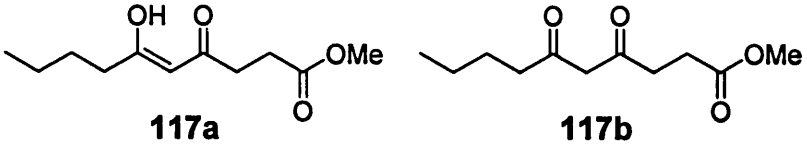
Preparation of (*E*)-1-(2-butyl-[1,3]dithiane-2-yl-5-hydroxymethyl-pent-3-en-2-one 116



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.013 mmol), acetone (2.0 mL), aldehyde **82** (30 mg, 0.13 mmol) and 2-butyne-1,4-diol (24 mg, 0.26 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **116** as a colourless oil (35 mg, 83%); ν_{max} (film)/cm^{-1} 2921, 2860, 1653, 950; δ_H (300 MHz; $CDCl_3$) 6.65 (1H, tt, *J* 3.7, 1.4, C*CH*), 4.50 (2H, td, *J* 1.9, 1.4, *CH*$_2$OH), 4.37 (2H, dt, *J* 3.7, 1.9, *CH*$_2$OH), 3.16 (2H, s, C*CH*$_2$CO), 2.84-2.69 (4H, m, S*CH*$_2$CH$_2$*CH*$_2$S), 2.08-2.02 (2H, m, SCH$_2$*CH*$_2$CH$_2$S), 1.94-1.87 (2H, m, *CH*$_2$CH$_2$CH$_2$CH$_3$), 1.41-1.24 (4H, m, CH$_2$*CH*$_2$*CH*$_2$CH$_3$) 0.86 (3H, t, *J* 7.1, CH$_2$CH$_2$CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 195.7, 143.2, 140.3, 60.6, 59.7, 50.9, 43.8, 38.0, 26.4, 24.9, 23.6, 22.8, 14.0; *m/z* (EI) 304 (30%, $[M]^+$), 273 (100% [M-

$CH_2OH]^+$), 217 (70% $[M\text{-}CH_2OHCCHCH_2OH]^+$); found $[M+H]^+$ 304.4705, $C_{14}H_{25}O_3S_2$ requires 304.4706.[112]

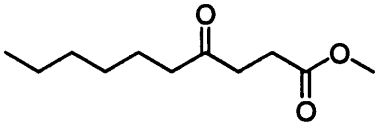
Preparation of (*Z*)-methyl 6-hydroxyl-4-oxodec-5-enoate 117a and methyl 4,6-dioxodecanoate 117b



117a **117b**

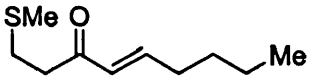
5-(2-Butyl-[1,3]dithian-2-yl)-4-oxo-pentanoic acid methyl ester (**91**) (50 mg, 0.18 mmol) in MeCN (2.0 mL) was added to a solution of NBS (190 mg, 1.07 mmol), $AgNO_3$ (112 mg, 0.67 mmol) and 2,6-lutidiene (39 μL, 0.33 mmol) in MeCN (5.0 mL) and water (1.2 mL) at 0 °C. The resulting solution was stirred for 30 minutes then warmed to room temperature. The reaction was diluted with EtOAc (20 mL), washed with ammonium chloride (sat. aq.) (20 mL), sodium sulfate (sat. aq.) (20 mL), brine (20 mL) and water (20 mL). It was then purified by flash chromatography (1:4 EtOAc: Petrol) to yield the title compounds as an inseperable mixture (2:1, **117a:117b)** as a pale yellow oil (35 mg, 76%); ν_{max} (film)/cm^{-1} 3420, 1736, 1719, 1709, 1466, 1264, 733; δ_H (300 MHz; $CDCl_3$) ((*Z*)-methyl 6-hydroxyl-4-oxodec-5-enoate **117a**) 15.18 (1H, br.s, *OH*), 5.51 (1H, s, *CH*), 3.69 (3H, s, O*Me*), 2.66-2.59 (4H, m, $CO\mathit{CH_2CH_2}CO_2Me$), 2.26 (2H, t, *J* 7.4, $C\mathit{CH_2}CH_2CH_2CH_3$), 1.63-1.51 (2H, m, $CCH_2\mathit{CH_2}CH_2CH_3$), 1.42-1.25 (2H, m, $CCH_2CH_2\mathit{CH_2}CH_3$), 0.92 (3H, t, *J* 7.3, $CCH_2CH_2CH_2\mathit{CH_3}$); δ_H (300 MHz; $CDCl_3$) (methyl 4,6-dioxodecanoate **117b**) 3.68 (3H, s, O*Me*), 3.61 (2H, s, $CO\mathit{CH_2}CO$), 2.66-2.59 (2H, m, $CO\mathit{CH_2}CH_2CO_2Me$), 2.83 (2H, t, *J* 6.7, $COCH_2\mathit{CH_2}CO_2Me$), 2.52 (2H, t, *J* 6.7, $C\mathit{CH_2}CH_2CH_2CH_3$), 1.63-1.51 (2H, m, $CCH_2\mathit{CH_2}CH_2CH_3$) 1.42-1.25 (2H, m, $CCH_2CH_2\mathit{CH_2}CH_3$), 0.90 (3H, t, *J* 7.3, $CCH_2CH_2CH_2\mathit{CH_3}$); δ_C (75 MHz; $CDCl_3$) (both) 204.5, 202.8, 195.6, 191.1, 173.4, 173.3, 99.5, 57.6, 52.2, 43.9, 38.5, 37.5, 34.2, 30.1, 29.2, 28.4, 28.0, 25.9, 22.7, 22.6, 14.2, 14.1; *m/z* (EI) 214 (60%, $[M]^+$), 155 (100% $[M\text{-}COOMe]^+$), 99 (50% $[M\text{-}MeCOOCH_2CH_2CO]^+$); found $[M+H]^+$ 214.2584, $C_{11}H_{18}O_4$ requires 214.2582.[112]

Preparation of dodecane-3,6-dione 118



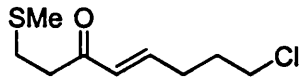
5-(2-Butyl-[1,3]dithian-2-yl)-4-oxo-pentanoic acid methyl ester (**91**) (30 mg, 0.1 mmol) in EtOH (5 mL) raney-nickel (0.5 g) was added. The resulting mixture was heated to reflux for 4 hours and then cooled to room temperature. The reaction was filtered though celite and purified by flash chromatography (1:4 EtOAc: Petrol) to yield the title compound (**118**) as a colouless oil (19 mg, 98%); ν_{max} (film)/cm^{-1} 3200, 1740, 1704, 1250, 721; δ_H (300 MHz; $CDCl_3$) 3.67 (O*Me*), 2.82-2.56 (4H, m, CO*CH*$_2$*CH*$_2$CO), 2.42 (2H, t, *J* 7.6, *CH*$_2$COCH$_2$), 1.76- 0.74 (11H, m, *CH*$_3$*CH*$_2$*CH*$_2$*CH*$_2$*CH*$_2$); δ_C (75 MHz; $CDCl_3$) 211.3, 173.5, 54.2, 42.3, 37.6, 31.4, 28.5, 27.2, 24.4, 23.8, 14.5. Data consistent to that reported in literature.[3]

Preparation of (*E*)-1-methylthio-non-4-en-3-one 122



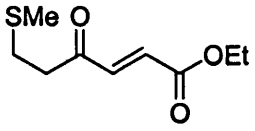
The general procedure for the hydroacylation reaction (**C**) was followed employing acetone (2.0 mL), pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol), 1-hexyne (160 μL, 4.5 mmol). The resulting mixture was stirred and heated at 55 °C for 1 hour. Flash chromatography (1:4 EtOAc:Petrol) yielded the title compound **122** as a yellow oil (54 mg, 98%); ν_{max} (film)/cm^{-1} 3049, 1704, 1658, 1421, 1267, 733; δ_H (300 MHz; $CDCl_3$) 6.86 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.10 (1H, dt, *J* 15.9, 1.4, CO*CH*CH), 2.87-2.73 (4H, m, MeS*CH*$_2$*CH*$_2$), 2.26-2.18 (2H, m, *CH*$_2$CH$_2$CH$_2$CH$_3$), 2.12 (3H, s, SMe), 1.48-1.30 (4H, m, CH$_2$*CH*$_2$*CH*$_2$CH$_3$), 0.91 (3H, t, *J* 7.2, CH$_2$CH$_2$CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 198.4, 148.1, 129.9, 39.6, 32.1, 30.0, 28.2, 22.1, 15.7, 13.7; *m/z* (EI) 186 (20%, [M]$^+$), 129 (40%, [M-$C_3H_6CH_3$]$^+$), 55 (100%, [M-MeSCH$_2$CH$_2$COCHCH$_3$]$^+$); found [M]$^+$ 186.1073, $C_{10}H_{18}O$ requires 186.1073; Anal. Calc. for $C_{10}H_{18}OS$: C, 64.46, H, 9.74. Found C, 64.0, H, 9.80%.[116]

Preparation of (*E*)-8-chloro-2-methylthio-oct-4-en-3-one 123



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 5-chloro-1-pentyne (158 μL, 1.5 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **123** as a yellow oil (53 mg, 85%); ν_{max} (film)/cm^{-1} 3049, 1632, 1416, 1252, 733; δ_H (300 MHz; $CDCl_3$) 6.83 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.17 (1H, dt, *J* 15.9, 1.5, CO*CH*CH), 3.56 (2H, t *J* 6.4, $CH_2CH_2CH_2Cl$), 2.88-2.74 (4H, m, $MeSCH_2CH_2$), 2.45-2.37 (2H, m, $CH_2CH_2CH_2Cl$), 2.12 (3H, s, MeS), 1.99-1.91 (2H, m, $CH_2CH_2CH_2Cl$); δ_C (75 MHz; $CDCl_3$) 197.7, 145.1, 130.3, 43.5, 39.6, 30.2, 29.0, 27.8, 15.4; ν_{max} (film) /cm^{-1} 1669 (C=O), 735 (C-Cl); *m/z* (EI) 206 (20%, $[M]^+$), 159 (60% $[M\text{-}OCO]^+$), 131 (100%, $[M\text{-}CH_4CO_2Me]^+$); found $[M]^+$ 206.0527, $C_9H_{15}ClOS$ requires 206.0527; Anal. Calc. for $C_9H_{15}ClOS$: C, 52.29, H, 7.31. Found C, 52.6, H, 7.31%.[116]

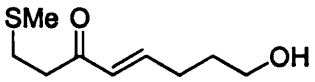
Preparation of (*E*)-6-methylthio-4-oxo-hex-2-enoic acid ethyl ester 124



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionnaldehyde **61** (30 μL, 0.3 mmol) and ethyl propiolate (152 μL, 1.5 mmol). Heated at 55 °C for 1 hour. Flash chromatography (DCM) yielded the title compound **124** as a yellow oil (44 mg, 73%); ν_{max} (film)/cm^{-1} 2930, 1697 1629, 1245, 1030; δ_H (300 MHz; $CDCl_3$) 7.00 (1H, d, *J* 16.0, CO*CH*CH), 6.63 (1H, d, *J* 16.0, COCH*CH*), 4.20 (2H, q, *J* 7.1, $COOCH_2CH_3$), 2.89 (2H, t, *J* 7.5, $MeSCH_2CH_2$), 2.73 (2H, t, *J* 7.5, $MeSCH_2CH_2$), 2.06 (3H, s, MeS), 1.26 (3H, t, *J* 7.1, $COOCH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 198.2, 165.8, 139.3, 131.7, 61.9, 41.7, 28.2, 16.3, 14.5; *m/z* (EI)

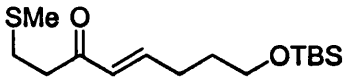
202 (15%, $[M]^+$), 157 (40%, $[M\text{-}OCH_2CH_3]^+$), 61 (100%, $[M\text{-}MeSCH_2CH_2COCHCHC]^+$); found $[M]^+$ 202.0658, $C_9H_{14}O_3S$ required 202.0655.[116]

Preparation of (*E*)-8-hydroxy-1-methylthio-oct-4-en-3-one 133



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 4-pentyn-1-ol (56 μL, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:1, EtOAc:Petrol) yielded the title compound **133** as a colourless oil (54 mg, 95%); ν_{max} (film)/cm^{-1} 3415, 2921, 1669, 1618, 1399, 1051; δ_H (300 MHz; $CDCl_3$) 6.86 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.12 (1H, dt, *J* 15.9, 1.5, CO*CH*CH), 3.65 (2H, t, *J* 6.3, $CH_2CH_2CH_2OH$), 2.86-2.81 (2H, m, $MeSCH_2CH_2$), 2.76-2.71 (2H, m, $MeSCH_2CH_2$), 2.35-2.28 (2H, m, $CH_2CH_2CH_2Cl$), 2.10 (3H, s, *Me*S), 1.86 (1H, br. s, O*H*), 1.76-1.67 (2H, m, $CH_2CH_2CH_2Cl$); δ_C (75 MHz; $CDCl_3$) 197.9, 146.7, 129.6, 61.2, 39.1, 30.2, 28.2, 27.6, 15.1; *m/z* (EI) 188 (3%, $[M]^+$), 140 (80%, $[M\text{-}MeSH]^+$) 71 (100% $[M\text{-}MeSCH_2CH_2CO]^+$); found $[M]^+$ 218.0968, $C_{10}H_{18}O_3S$ requires 218.0971.[116]

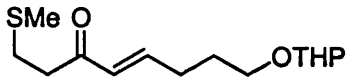
Preparation of (*E*)-8-(*tert*-butyl-dimethyl-silanyloxy-1-methylthio-oct-4-en-3-one 134



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and *t*-butyl-dimethyl-pent-4-ynyloxy-silane (136 mg, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:3, EtOAc:Petrol) yielded the title compound **134** as a pale yellow oil (81 mg, 89%); ν_{max} (film)/cm^{-1} 2921, 1653, 1345, 667; δ_H (300 MHz; $CDCl_3$) 6.86 (1H. dt, *J* 15.9, 6.9, COCH*CH*), 6.09 (1H, dt, *J* 15.9, 1.5, CO*CH*CH), 3.60 (2H, t, *J* 6.1, $CH_2CH_2CH_2OTBS$), 2.85-2.71 (4H, m, $MeSCH_2CH_2$), 2.32-2.24 (2H, m, $CH_2CH_2CH_2OTBS$), 2.09 (3H, s, MeS), 1.70-1.61 (2H, m, $CH_2CH_2CH_2OTBS$), 0.86

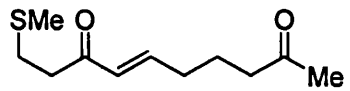
(9H, s, $SiC(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$); δ_C (75 MHz; $CDCl_3$) 197.8, 147.1, 129.5, 61.5, 39.1, 30.4, 28.4, 27.6, 25.2, 17.6, 15.2, -5.9; *m/z* (CI +) 303 (100%, $[M+H]^+$), 255 (40%, $[M\text{-}MeS]^+$); found $[M]^+$ 303.1809, $C_{15}H_{30}O_2SSi$ requires 303.1809.[116]

Preparation of (*E*)-1-methylthio-8-(tetrahydro-pyran-2-yloxy)-oct-4-en-3-one 135



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 2-pent-4-ynyloxy-tetrahydro-pyran (118 mg, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:3, EtOAc:Petrol) yielded the title compound **135** as a pale yellow oil (76 mg, 93%); ν_{max} (film)/cm^{-1} 2961, 2865, 1686, 1276, 911; δ_H (300 MHz; $CDCl_3$) 6.88 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.11 (1H, dt, *J* 15.9, 1.5, CO*CH*CH), 4.55 (1H, t, *J* 3.0, O*CH*-THP), 3.87-3.71 (2H, m, OCH_2-THP), 3.52-3.36 (2H, m, $CH_2CH_2CH_2O$), 2.87-2.71 (4H, m, $MeSCH_2CH_2$), 2.36-2.29 (2H, m, $CHCH_2$-THP), 2.10 (3H, s, *Me*S), 1.83-1.69 (4H, m, $CHCHCH_2CH_2$ and $CHCH_2$-THP), 1.58-1.47 (4H, m, $CHCHCH_2CH_2$ and $CHCH_2CH_2$-THP); δ_C (75 MHz; $CDCl_3$) 198.3, 147.3, 130.0, 98.7, 66.3, 62.2, 39.5, 30.4, 29.2, 28.1, 27.9, 25.2, 19.4, 15.6; *m/z* (EI) 272 (5%, $[M]^+$), 225 (40%, $[M\text{-}MeS]^+$), 172 (80%, $[M\text{-}OTHP]^+$), 169 (100% $[M\text{-}MeSCH_2CH_2CO]^+$); found $[M]^+$ 272.1442, $C_{14}H_{24}O_3S$ requires 272.1446.[116]

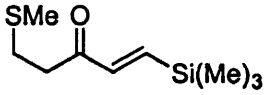
Preparation of (*E*)-10-methylthio-dec-6-ene-2,8-dione 136



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and hept-6-yn-2-one (66 mg, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol)

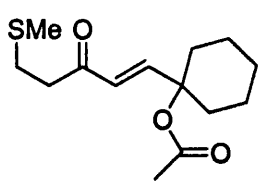
yielded the title compound **136** as a yellow oil (44mg, 69%); ν_{max} (film)/cm^{-1} 3049, 2978, 2295, 1704, 1673, 1617, 1411, 1252, 903, 744; δ_H (300 MHz; $CDCl_3$) 6.82 (1H, dt, *J* 15.9, 6.6, CH*CH*CH_2), 6.11 (1H, dt, *J* 15.9, 1.5, *CH*$CHCH_2$), 2.88-2.74 (4H, m, MeS*CH_2CH_2*), 2.47 (2H, t, *J* 7.2, $CH_2CH_2CH_2CO$), 2.28-2.20 (2H, m, *CH_2*CH_2CH_2CO), 2.14 (3H, s, $CO*CH_3*$), 2.12 (3H, s, MeS), 1.81-1.71 (2H, m, CH_2*CH_2*CH_2CO); δ_C (75 MHz; $CDCl_3$) 207.8, 198.1, 146.6, 130.3, 42.3, 39.6, 31.4, 29.8, 28.0, 21.6, 15.6; *m/z* (EI+) 214 (5%, $[M]^+$), 73 (90%, $[M-COCHCH(CH_2)_3COCH_3]^+$), 59 (100%, $[M-CH_2COCHCH(CH_2)_3COCH_3]^+$); found 214.1022 $[M]^+$ $C_{11}H_{18}O_2S$ requires 214.1022.[116]

Preparation of (*E*)-5-methylthio-1-trimethylsilanyl-pent-1-en-3-one 137



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and (trimethylsilyl)acetylene (85 μL, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **137** as a pale yellow oil (53 mg, 89%); ν_{max} (film)/cm^{-1} 2957, 1678, 1432, 1250, 995, 836; δ_H(300 MHz, $CDCl_3$) 7.06 (1H, d, *J* 19.2, COCH*CH*), 6.45 (1H, d, *J* 19.2, CO*CH*CH), 2.92-2.87 (2H, m, $MeSCH_2$*CH_2*), 2.77-2.72 (2H, m, MeS*CH_2*CH_2), 2.10 (3H, s, MeS), 0.12 (9H, s, $Si(Me)_3$); δ_C(75 MHz, $CDCl_3$) 198.4, 147.4, 141.8, 39.1, 28.1, 15.8, -1.9; *m/z* (EI+) 202 (10%, $[M]^+$), 139 (40%, $[M-MeSCH_2CH_2]^+$), 73 (80%, $[M- MeSCH_2CH_2COCHCH]^+$); found 203.0918 $[M+H]^+$ $C_9H_{19}OSSi$ requires 203.0920.[116]

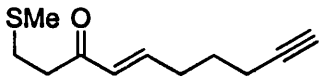
Preparation of *(E)*-1-(5-(methylthio)-3-oxopent-1-enyl)cyclohexyl acetate 138



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 1-ethylnlcyclohexyl

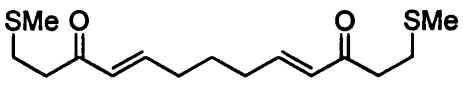
acetate (100 mg, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **138** as a pale yellow oil (64 mg, 79%); ν_{max} (film)/cm^{-1} 2900, 1745, 1650, 1464, 970; δ_H (300 MHz; $CDCl_3$) 6.92 (1H, d, *J* 16.5, COCH*CH*), 6.02 (1H, d, *J* 16.5, CO*CH*), 2.85-2.79 (2H, m, *CH*$_2$CO), 2.73-2.67 (2H, m, MeS*CH*$_2$), 2.14-2.10 (2H, m, C*CH*$_2$ cyc), 2.06 (3H, s, *Me*S), 1.99 (3H, s, CO*CH*$_3$), 1.54-1.41 (8H, m, 4 × *CH*$_2$ cyc); δ_C (75 MHz; $CDCl_3$) 198.3, 169.4, 149.6, 126.7, 80.1, 39.7, 34.3, 27.8, 24.7, 21.4, 21.2, 15.5; *m/z* (ES+) 269 (10%, $[M]^+$), 222 (40%, $[M\text{-}MeS]^+$), 166 (80%, $[M\text{- }MeSCH_2CH_2CO]^+$); found 269.1212 $[M+H]^+$ $C_{14}H_{23}O_3S$ requires 269.1210.[116]

Preparation of (*E*)-1-methylthio-dec-4-en-9-yn-3-one 139



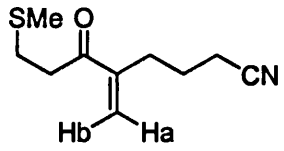
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 1,6-heptadiyne (104 μL, 0.9 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **139** as a pale yellow oil (44 mg, 74%); ν_{max} (film)/cm^{-1} 2976, 1652, 916, 731; δ_H (300 MHz; $CDCl_3$) 6.85 (1H, dt, *J* 15.9, 6.9, CH*CH*CH_2), 6.15 (1H, dt, *J* 15.9, 1.5, *CH*$CHCH_2$), 2.88-2.74 (4H, m, MeS*CH*$_2$*CH*$_2$), 2.40-2.32 (2H, m, *CH*$_2CH_2CH_2C$), 2.24 (2H, td, *J* 7.0, 2.6, CH_2CH_2*CH*$_2$C), 2.12 (3H, s, MeS), 1.98 (1H, t, *J* 2.6, *C*HC), 1.76-1.66 (2H, m); δ_C (75 MHz; $CDCl_3$) 198.3, 146.5, 131.0, 83.4, 69.1, 39.9, 31.2, 28.3, 26.7, 17.9, 15.8; *m/z* (EI+) 196 (5%, $[M]^+$), 181 (40%, $[M\text{-}CH_3]^+$), 81 (100%, $[M\text{-}CHC(CH_2)_4]^+$), 61 (90%, $[M\text{-}CHC(CH_2)_3\text{-}CHCHCOCH_2]^+$); found $[M+H]^+$ 197.0993, $C_{11}H_{17}OS$ requires 197.0995.[116]

Preparation of (4*E*, 9*E*)-1,13-*bis*(methaneulfonyl)trideca-4,9-diene-3,11-dione 140



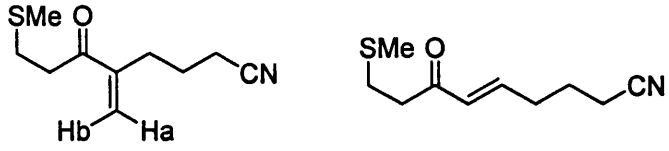
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methanesulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 1,6-heptadiyne (17 μL, 0.15 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **140** as a pale yellow oil (27 mg, 60%); ν_{max} (film)/cm^{-1} 2980,1700, 1650, 900; δ_H (300 MHz; $CDCl_3$ 6.8 (2H, dt, *J* 15.8, 6.98, 2 × COCH*CH*), 6.06 (2H, dt, *J* 15.8, 1.5, 2 × CO*CH*), 2.81-2.76 (4H, m, 2 × *CH_2*CO), 2.76-2.73 (4H, m, 2 × MeS*CH_2*) 2.24-2.16 (4H, m, CH*$CH_2CH_2CH_2$*), 2.06 (6H, s, 2 × *Me*S), 1.65-1.58 (2H, m, CH_2*CH_2*CH_2); δ_C (75 MHz; $CDCl_3$) 198.7, 146.9, 131.0, 40.4, 32.2, 28.7, 26.8, 16.3; *m/z* (CI+, NH_3) 318 (7%, $[M+NH_4]^+$), 272 (100%, $[M-SCH_3]^+$), 224 (30%, $[M-CH_3SCH_2CH_3]^+$); found $[M+H]^+$ 318.1557, $C_{15}H_{28}O_2N_1S_2$ requires 318.1556.[116]

Preparation of 5-(3-methylthio)-6-oxooctanenitrile 141a



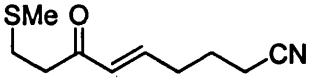
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 5-hexynenitrile (157 μL, 1.5 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:1, EtOAc:Petrol) yielded the title compound **141** as a yellow oil (41 mg, 68%); ν_{max} (film)/cm^{-1} 2967, 2337, 1646, 1551, 1123, 750; δ_H (300 MHz; $CDCl_3$) 6.04 (1H, s, CCH_a*H_b*), 5.83 (1H, t, *J* 1.0, CC*H_a*H_b), 2.94 (2H, t, *J* 7.0, $MeSCH_2$*CH_2*), 2.71 (2H, t, *J* 7.0, MeS*CH_2*CH_2), 2.37 (2H, td, *J* 7.3, 1.0, CH_2CH_2*CH_2*CN), 2.27 (2H, t, *J* 7.1, *CH_2*CH_2CH_2CN), 2.06 (3H, s, MeS), 1.79-1.69 (2H, m, CH_2*CH_2*CH_2CN); δ_C (75 MHz; $CDCl_3$) 199.9, 146.9, 126.5, 119.8, 37.9, 30.6, 29.1, 24.7, 17.1, 16.3; *m/z* (EI+) 197 (10%, $[M]^+$), 149 (40%, $[M-MeSH]^+$), 75 (100% $[M-COCCH_2(CH_2)_3CN]^+$); found $[M+H]^+$ 198.0945, $C_{10}H_{16}NOS$ requires 198.0945.[116]

Preparation of 5-(3-methylthio)-6-oxooctanenitrile 141a and (*E*)-9-methylthio-7-oxo-non-5-enenitrile 141b



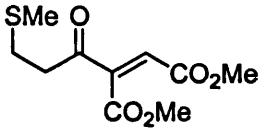
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde (30 μL, 0.3 mmol), MeCN (16 μL, 0.3 mmol) and 5-hexynenitrile (62 μL, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound as a yellow oil (48 mg, 81% 5:1 linear:branched); ν_{max} (film)/cm^{-1} (major linear) 2908, 2357, 1665, 1662, 1428; δ_H (300 MHz; $CDCl_3$) (major linear) 6.73 (1H, dt, *J* 15.9, 6.9, CCH*CH*), 6.13 (1H, d, *J* 15.9, C*CH*CH), 2.82-2.68 (4H, m, MeSCH_2CH_2), 2.38-2.31 (4H, m, CH$CH_2CH_2CH_2$CN), 2.06 (3H, s, MeS), 1.84-1.75 (2H, m, $CHCH_2CH_2CH_2CN$); δ_C (75 MHz; $CDCl_3$) (major linear) 196.8, 143.1, 130.1, 117.8, 39.0, 29.8, 27.0, 22.6, 15.5, 14.7; ν_{max} (film) /cm^{-1} (minor branched) 2967, 2337, 1646, 1551, 1123, 750; δ_H (300 MHz; $CDCl_3$) (minor branched) 6.04 (1H, s, CH_aH_b), 5.83 (1H, t, *J* 1.0, CH_aH_b), 2.94 (2H, t, *J* 7.0, $MeSCH_2CH_2$), 2.71 (2H, t, *J* 7.0, $MeSCH_2CH_2$), 2.37 (2H, td, *J* 7.3, 1.0, $CH_2CH_2CH_2CN$), 2.27 (2H, t, *J* 7.1, $CH_2CH_2CH_2CN$), 2.06 (3H, s, MeS), 1.79-1.69 (2H, m, $CH_2CH_2CH_2CN$); δ_C (75 MHz; $CDCl_3$) (minor branched) 199.9, 146.9, 126.5, 119.8, 37.9, 30.6, 29.1, 24.7, 17.1, 16.3; *m/z* (EI+) (major linear) 197 (5 %, $[M]^+$), 150 (40%, $[M\text{-}MeS]^+$), 121 (100%, $[M\text{-}(CH_2)_3CN]^+$), 75 (80% $[M\text{-}COCCH_2(CH_2)_3CN]^+$); found $[M+NH_4]^+$ 215.1213, $C_{10}H_{19}N_2OS$ requires 215.1213; *m/z* (EI+) (minor branched) 197 (10 %, $[M]^+$), 149 (40%, $[M\text{-}MeSH]^+$) 75 (100% $[M\text{-}COCCH_2(CH_2)_3CN]^+$); found $[M+H]^+$ 198.0945, $C_{10}H_{16}NOS$ requires 198.0945.[116]

Preparation of (*E*)-9-methylthio-7-oxo-non-5-enenitrile 141b



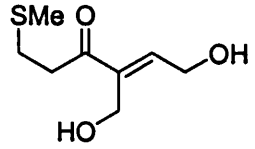
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde (30 μL, 0.3 mmol), MeCN (320 μL, 6.0 mmol) and 5-hexynenitrile (62 μL, 0.6 mmol). Heated at 55 °C for 4 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound as a yellow oil (44 mg, 75%). Data consistent to that reported earlier.

Preparation of (*E*)-2-(-3-methylthio-propionyl)-but-2-enedioic acid dimethyl ester 146



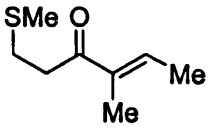
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and dimethyl acetylenedicarboxylate (158 μL, 1.5 mmol). Heated at 55 °C overnight. Flash chromatography (DCM) yielded the title compound **146** as a yellow oil (55 mg, 75% 2:1 Z:E); ν_{max} (film)/cm^{-1} 3427, 3011, 2966, 2489, 1731,1728, 1455, 1248, 1051; δ_H (300 MHz; $CDCl_3$) (major *Z*) 6.80 (1H, s, C*CH*), 3.83 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.03-2.96 (2H, m, $MeSCH_2CH_2$), 2.90-2.84 (2H, m, $MeSCH_2CH_2$), 2.14 (3H, s, MeS); (minor *E*) 6.72 (1H, s, C*CH*), 3.91 (3H, s, CO_2Me), 3.81 (3H, s, CO_2Me), 3.03-2.96 (2H, m, $MeSCH_2CH_2$), 2.77 (2H, t, *J* 7.3, $MeSCH_2CH_2$), 2.12 (3H, s, MeS); δ_C (75 MHz; $CDCl_3$) (*E* and *Z*) 199.6, 193.1, 164.7, 163.5, 163.4, 162.0, 145.7, 143.0, 127.7, 127.2, 52.2, 52.0, 51.8, 51.7, 41.8, 38.6, 26.6, 26.3, 14.9, 14.7; *m/z* (EI) 246 (10%, $[M]^+$), 167 (100%, $[M\text{-}MeSO_2]^+$); found $[M]^+$ 246.0556, $C_{10}H_{14}O_5S$ required 246.0555.[116]

Preparation of (*E*)-6-hydroxy-4-hydroxymethyl-1-methylthiohex-4-en-3-one 147



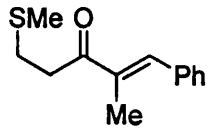
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 2-Butyne-1,4-diol (180 mg, 0.9 mmol). Heated at 55 °C overnight. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **147** as a yellow oil (48 mg, 85%); ν_{max} (film)/cm^{-1} 2921, 2860, 1653, 1354, 1043; δ_H (300 MHz; $CDCl_3$) 6.66 (1H, tt, *J* 3.7, 1.3, C*CH*CH_2), 4.50 (2H, dt, *J* 3.7, 2.0, C*CH*$_2$OH), 4.38 (2H, td, *J* 2.0, 1.3, CH*CH*$_2$OH), 2.87 (2H, t, *J* 7.1, MeSCH$_2$*CH*$_2$), 2.69 (2H, t, *J* 7.1, MeS*CH*$_2$CH$_2$), 2.05 (3H, s, MeS); δ_C (75 MHz; $CDCl_3$) 198.2, 142.0, 141.4, 61.1, 59.9, 37.9, 29.0, 16.3; *m/z* (EI+) 190 (10%, $[M]^+$), 143 (60%, $[M\text{-}MeS]^+$), 115 (100%, $[M\text{-}MeSCH_2CH_2]^+$), 87 (40%, $[M\text{-}MeSCH_2CH_2CO]^+$); found 191.5876 $[M+H]^+$ $C_8H_{15}O_3S$ requires 191.5874.[116]

Preparation of (*E*)-4-methyl-1-methylsulfanyl-hex-4-en-3-one 148



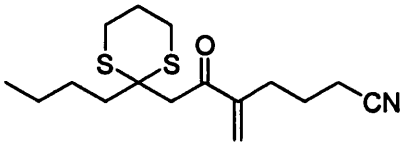
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 2-butyne (71 μL, 0.9 mmol). Heated at 55 °C overnight. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **148** as a pale yellow oil (36 mg, 76%); ν_{max} (film)/cm^{-1} 2916, 1663, 1421, 1242, 908, 723; δ_H (300 MHz; $CDCl_3$) 6.70 (1H, qq, *J* 6.9, 1.1, *CH*CH_3), 2.89 (2H, t, *J* 7.4, MeSCH$_2$*CH*$_2$), 2.70 (2H, t, *J* 7.4, MeS*CH*$_2$CH$_2$), 2.06 (3H, s, MeS), 1.81 (3H, d, *J* 6.9, *CH*$_3$CCH), 1.72 (3H, d, *J* 1.1, CH*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 200.1, 138.6, 138.2, 37.5, 29.5, 16.3, 15.3, 11.4; *m/z* (EI) 158 (10%, $[M]^+$), 110 (100%, $[M\text{-}CH_3SH]^+$), 83 (80%, $[M\text{-}MeSCH_2CH_2]^+$), 61 (40%, $[M\text{-}CH_3CHC(CH_3)COCH_2]^+$); found $[M]^+$ 158.0760, $C_8H_{14}OS$ requires 158.0760.[116]

Preparation of (*E*)-2-methyl-5-(methylthio)-1-phenylpent-1-en-3-one 149



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (5 mg, 0.0075 mmol), acetone (1.5 mL), 3-methylsulfanyl propionaldehyde **61** (15 μL, 0.15 mmol) and 1-phenyl-1-propyne (56 μL, 0.45 mmol). Heated at 55 °C overnight. Flash chromatography (1:4, EtOAc:Petrol) yielded the title compound **149** as a pale yellow oil (22 mg, 67%); ν_{max} (film)/cm^{-1} 2916, 2346, 1668, 1647, 1432, 1267, 1047, 728; δ_H (300 MHz; $CDCl_3$) 7.54 (1H, q, *J* 1.4, $CHCH_3$), 7.43-7.35 (5H, m, Ar), 3.14 (2H, t, *J* 7.6, $MeSCH_2\mathit{CH_2}$), 2.85 (2H, t, *J* 7.6, $MeS\mathit{CH_2}CH_2$), 2.17 (3H, s, MeS), 2.07 (3H, d, *J* 1.4, $CH\mathit{CH_3}$); δ_C (75 MHz; $CDCl_3$) 200.2, 138.8, 137.0, 135.5, 129.5, 128.4, 128.3, 37.4, 28.9, 15.7, 12.9; *m/z* (EI+) 220 (20%, $[M]^+$) 172 (10%, $[M\text{-}MeSH]^+$); found 221.0996 $[M+H]^+$ $C_{13}H_{17}OS$ requires 221.0995.[116]

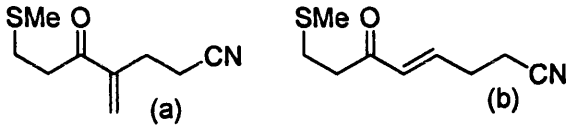
Preparation of (*E*)-5-[2-(2-butyl-1,3-dithiane-2-yl)-acetyl]-hex-5-enitrile 150



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.013 mmol), acetone (2.0 mL), [1,3]dithiolan-2-yl-acetaldehyde **93** (30 mg, 0.13 mmol) and 5-hexynenitile (27 μL, 0.26 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:4 EtOAc:Petrol) yielded the title compound **150** as a yellow oil (28 mg, 68%); ν_{max} (film)/cm^{-1} 3744, 2361, 1653, 1265; δ_H (300 MHz; $CDCl_3$) 6.10 (1H, s, $COC\mathit{CH_a}H_b$), 5.87 (1H, s, $COCCH_a\mathit{H_b}$), 3.28 (2H, s, $C\mathit{CH_2}CO$), 2.85-2.82 (4H, m, $S\mathit{CH_2}CH_2\mathit{CH_2}S$), 2.50 (2H, t, *J* 7.2, $\mathit{CH_2}CN$), 2.34 (2H, t, *J* 7.2, $C\mathit{CH_2}CH_2CH_2CN$), 2.11-2.06 (2H, m, $C\mathit{CH_2}CH_2CH_2CH_3$), 2.02-1.96 (2H, m, $CCH_2\mathit{CH_2}CH_2CN$), 1.87-1.82 (2H, m, $SCH_2\mathit{CH_2}CH_2S$), 1.61-1.50 (2H, m, $CCH_2\mathit{CH_2}CH_2CH_3$), 1.43-1.42 (2H, m, $CCH_2CH_2\mathit{CH_2}CH_3$), 0.94 (3H, t, *J* 7.2, $CCH_2CH_2CH_2\mathit{CH_3}$); δ_C (75 MHz; $CDCl_3$) 197.6, 148.4, 125.7, 119.6, 51.1, 43.4, 38.4, 30.6, 26.6, 26.5, 25.0, 24.3, 22.9, 16.8, 14.2; *m/z* (EI) 312 (60 %, $[M]^+$), 255 (90% $[M\text{-}CH_3CH_2CH_2CH_2]^+$), 218 (80% [M-

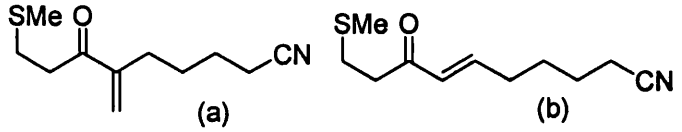
$CNCH_2CH_2CH_2CCH_2]^+$); found $[M+H]^+$ 312.5155, $C_{16}H_{26}NOS_2$ requires 312.5158.[112]

Preparation of (*E*)-8-methylthio-6-oxooct-4-enenitrile (b) and 4-methylene-7-(methylthio)-5-oxoheptanenitrile (a) 154



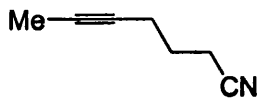
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 4-cyano-1-butyne (50 mg, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded 8-methylsulfanyl-6-oxo-oct-4-enenitrile (**154b**) as a pale yellow oil (25 mg, 46%) ν_{max} (film)/cm^{-1} 3049, 2295, 1668, 1411, 1252, 893, 728; δ_H (300 MHz; $CDCl_3$) 6.74 (1H, dt, *J* 15.9, 6.4, COCH*CH*), 6.17 (1H, d, *J* 15.9, CO*CH*), 2.82 (2H, t, *J* 6.5, CH_2CN), 2.71 (2H, t, *J* 6.5, CH_2CO), 2.57-2.46 (4H, m, MeSCH_2 and CHCH_2), 2.06 (3H, s, *Me*S); δ_C (75 MHz; $CDCl_3$) 196.6, 140.4, 130.6, 117.3, 39.3, 26.9, 26.8, 15.1, 14.7; *m/z* (EI) 183 (7%, [M]), 135 (50%, $[M-MeSH]^+$), 108 (90%, $[M-MeSCH_2CH_2]^+$), 75 (100%, $[M-CNCH_2CH_2CCCO]^+$), 54 (80%, $[M-MeSCH_2CH_2COCCCH_2]^+$); found $[M]^+$ 183.0713, $C_9H_{13}NOS$ requires 183.0712 and 4-(3-methylsulfanyl-propionyl)-pent-4-enenitrile (**154a**) as a pale yellow oil (17 mg, 31%); δ_H (300 MHz; $CDCl_3$) 6.22 (1H, s, C*CH*H), 6.04 (1H, s, C*CH*H), 3.06 (2H, t, *J* 7.3, CH_2CN), 2.77 (2H, t, *J* 7.3, CH_2CO), 2.63-2.52 (4H, m, MeSCH_2 and COCCH_2), 2.13 (3H, s, *Me*S); δ_C (75 MHz; $CDCl_3$) 198.5, 143.7, 127.2, 118.3, 36.7, 27.8, 26.9, 16.2, 15.2.[116]

Preparation of (*E*)-10-methylthio-8-oxodec-6-enenitrile (b) and 6-methylene-9-(methylthio)-7-oxononanenitrile (a) 155



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and hept-6-ynenitrile (64 mg, 0.6 mmol). Heated at 55 °C for 1 hour. Flash chromatography (1:4, EtOAc:Petrol) yielded 10-Methylsulfanyl-8-oxo-dec-6-enenitrile (**155b**) as a pale yellow oil (31 mg, 49%) ν_{max} (film)/cm^{-1} 3049, 2978, 1673, 1416, 1252, 887, 744; δ_H (300 MHz; $CDCl_3$) 6.76 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.08 (1H, dt, *J* 15.9, 1.5, CO*CH*), 2.82-2.68 (4H, m, CH_2CH_2CO), 2.32 (2H, t, *J* 6.7, CH_2CN), 2.26-2.19 (2H, m, $CHCH_2$), 2.06 (3H, s, *Me*S), 1.69-1.56 (4H, m, $CHCH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 197.6, 145.4, 130.0, 118.7, 39.3, 30.8, 27.6, 26.3, 24.2, 16.4, 15.2; *m/z* (ES+) 211 (5%, $[M]^+$), 164 (30%, $[M\text{-}MeS]^+$), 74 (80%, $[M\text{-}CN(CH_2)_4CHCHCOH]^+$), 55 (100%, $[M\text{-}CH_3CH_2CN]^+$) ; found 212.1099 $[M+H]^+$ $C_{11}H_{17}NOS$ requires 212.1104 and 6-(3-methylsulfanyl-propionyl)-hept-6-enenitrile (**155a**) as a colourless oil (20 mg, 32%); δ_H (300 MHz; $CDCl_3$) 6.06 (1H, s, COCC*H*H), 5.82 (1H, s, COCCH*H*), 3.00 (2H, t, *J* 6.9, CH_2CO), 2.77 (2H, t, *J* 6.9, $MeSCH_2$), 2.42-2.26 (4H, m, $CHCH_2CH_2CH_2CH_2CN$), 2.13 (3H, s, *Me*S), 1.70-1.54 (4H, m, $CHCH_2CH_2CH_2CH_2CN$); δ_C (75 MHz; $CDCl_3$) 200.2, 148.1, 125.5, 120.0, 38.0, 30.4, 29.1, 28.0, 25.5, 17.4, 16.3.[116]

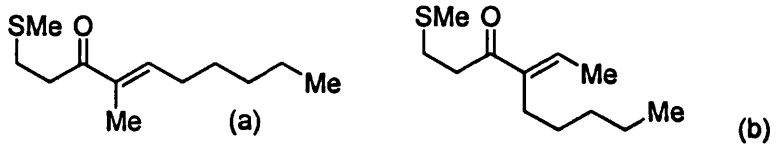
Preparation of hept-5-ynenitrile 157



To NaCN (0.5g, 0.011 mol) in EtOH (10.5 mL) and water (3.0 mL) 6-chlorohex-2-yne (1.16g, 0.01 mol) was added. The resulting solution was heated at reflux overnight. It was then cooled to room temperature diluted with DCM (50 mL). The solution was extracted with water (3 × 50 mL) and dried ($MgSO_4$). After this time the solution was reduced *in vacuo* and purified by flash chromatography (1:9

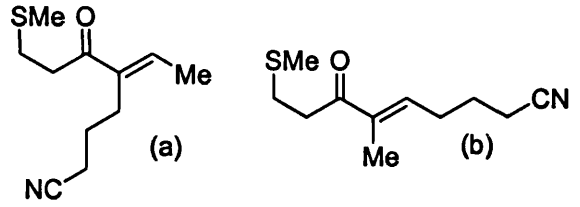
EtOAc:Petrol) giving the title compound **157** as a colourless oil (0.95 g, 89%); ν_{max} (film)/cm^{-1} 2921, 2243, 1422, 1267, 749; δ_H (300 MHz; $CDCl_3$) 2.42 (2H, t, *J* 7.2, $CH_2CH_2CH_2CN$), 2.28-2.21 (2H, m, $CH_2CH_2CH_2CN$), 1.81-1.74 (2H, m, $CH_2CH_2CH_2CN$), 1.72 (3H, t, *J* 2.5, CH_3CC); δ_C (75 MHz; $CDCl_3$) 119.3, 77.6, 76.2, 24.8, 17.8, 16.0, 3.4; *m/z* (EI) 107 (10%, $[M]^+$), 106 (100%, $[M-H]^+$), 79 (40%, $[M-H_2CN]^+$), 53 (50%, $[M-CH_3CCCH_2]^+$), 41 (70%, $[M-CNCH_2CH_2C]^+$); found $[M-H]^+$ 106.0651, C_7H_9N requires 106.0651.[116]

Preparation of (*E*)-4-methyl-1-(methylthio)dec-4-en-3-one (a) and (*E*)-4-ethylidene-1-(methylthio)nonan-3-one (b) 158



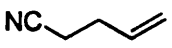
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and 2-octyne (87 μL, 0.6 mmol). Heated at 55 °C for 48 hours. Flash chromatography (1:4, EtOAc:Petrol) yielded an unseperable mixture of the title compounds **158a and 158b** as a colourless oil (37 mg, 58%, 3:1 a:b); ν_{max} (film)/cm^{-1} (both) 2921, 2854, 2253, 1663, 1468, 1375, 903, 723; δ_H (300 MHz; $CDCl_3$) ((*E*)-4-methyl-1-(methylthio)dec-4-en-3-one (a)) 6.58 (1H, td, *J* 7.2, 1.2, CH_3CCH), 2.93-2.88 (2H, m, $MeSCH_2CH_2$), 2.73-2.67 (2H, m, $MeSCH_2CH_2$), 2.24-2.14 (2H, m, $CHCH_2$), 2.06 (3H, s, MeS), 1.71 (3H, br. s, CH_3CCH), 1.45-1.36 (2H, m, $CH_2CH_2CH_3$), 1.28-1.20 (4H, m, $CH_2CH_2CH_2CH_3$), 0.86-0.78 (3H, m, CH_2CH_3) (minor b) 6.66 (1H, q, *J* 7.0, $CCHCH_3$), 2.93-2.88 (2H, m, $MeSCH_2CH_2$), 2.73-2.67 (2H, m, $MeSCH_2CH_2$), 2.24-2.14 (2H, m, $CHCH_2$), 2.05 (3H s, MeS), 1.76 (3H, d, *J* 7.0, $CCHCH_3$), 1.45-1.36 (6H, m, $CH_2CH_2CH_2CH_2CH_3$); δ_C (75 MHz; $CDCl_3$) (both) 199.6, 199.3, 143.2, 142.9, 137.4, 136.8, 37.0, 36.9, 31.7, 31.4, 28.9, 28.8, 28.4, 28.1, 25.1, 22.3, 22.2, 15.7, 14.5, 13.83, 13.78, 11.1; *m/z* (EI+) 214 (20%, $[M]^+$), 166 (95%, $[M-MeSH]^+$), 109 (100%, $[M-MeS(CH_2)_2COH]^+$); found 214.1385 $[M]^+$ $C_{12}H_{22}OS$ requires 214.1386.[116]

Preparation of (*E*)-5-ethylidene-8-(methylthio)-6-oxooctanenitrile (a) and (*E*)-6-methyl-9-methylthio-7-oxonon-5-enenitrile (b) 159



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (2.0 mL), 3-methylsulfanyl propionaldehyde **61** (30 μL, 0.3 mmol) and hept-5-ynenitrile (64 mg, 0.6 mmol). Heated at 55 °C overnight. Flash chromatography (1:4, EtOAc:Petrol) yielded 5-(3-Methylsulfanyl-propionyl)-hept-5-enenitrile (a) (33 mg, 53 %) ν_{max} (film) /cm^{-1} 2926, 1673, 1432, 1252, 733; δ_H (300 MHz; $CDCl_3$) 6.85 (1H, q, *J* 7.0, C*CH*CH_3), 2.95 (2H, t, *J* 6.8, $MeSCH_2CH_2$), 2.76 (2H, t, *J* 6.8, $MeSCH_2CH_2$), 2.45 (2H, t, *J* 7.6, $NCCH_2CH_2$), 2.32 (2H, t, *J* 7.1, $NCCH_2CH_2CH_2$), 2.12 (3H, s, MeS), 1.94 (3H, d, *J* 7.0, $CCHCH_3$), 1.76-1.66 (2H, m, $NCCH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 199.0, 140.6, 139.6, 119.5, 36.7, 28.8, 24.3, 24.0, 16.8, 15.7, 14.7; *m/z* (EI) 211 (10%, $[M]^+$), 162 (100%, $[M\text{-}CH_3SH_2]^+$), 108 (80%, $[M\text{-}CH_3CHC(CH_2)_3CN]^+$), 75 (50%, $[M\text{-}COCH_3CHC(CH_2)_3CN]^+$); found [M] 211.1024, $C_{11}H_{17}NOS$ requires 211.1025; and 6-methyl-9-methylsulfanyl-7-oxo-non-5-enenitrile (b) (17 mg, 27%); ν_{max} (film) /cm^{-1} 2920, 1650, 1454, 1234, 722; δ_H (300 MHz; $CDCl_3$) 6.56 (1H, tq, *J* 7.2, 1.3, CH_3CCH), 2.96 (2H, t, *J* 7.1, $MeSCH_2CH_2$), 2.77 (2H, t, *J* 7.1, $MeSCH_2CH_2$), 2.47-2.38 (4H, m, $CH_2CH_2CH_2CN$), 2.13 (3H, s, MeS), 1.91-1.81 (5H, m, CH_3CCH and $CH_2CH_2CH_2CN$); δ_C (75 MHz; $CDCl_3$) 199.3, 138.8, 138.6, 118.8, 37.1, 28.7, 27.5, 24.2, 16.6, 15.7, 11.4; *m/z* (EI) 211 (5%, M), 162 (100%, M-CH_3SH_2), 108 (80%, M-$CH_3CHC(CH_2)_3CN$), 75 (40%, M-$COCH_3CHC(CH_2)_3CN$); found [M] 211.1023, $C_{11}H_{17}NOS$ requires 211.1025.[116]

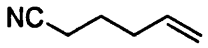
The general procedure for the synthesis of nitrile compounds (E) as exemplified by pent-4-enenitrile 160



To 4-bromobutene (2.5 g, 19 mmol) in EtOH (26 mL) and H_2O (7.5 mL) was added NaCN (1.0 g, 20 mmol) and the resulting mixture was heated at reflux for 16 hours.

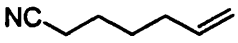
The reaction was then cooled to room temperature and quenched with 1 M NaOH (aq) (20 mL). The product was extracted with Et_2O (3 × 30 mL), the organic extracts combined and dried ($MgSO_4$) and reduced *in vacuo*. Flash chromatography (1:9 Et_2O: petrol) to yield the title compound **160** as a colourless oil (1.38g, 90%). ν_{max} (film)/cm^{-1} 3530, 2870, 1810, 1590, 1480, 99; δ_H (300 MHz; $CDCl_3$) 5.83-5.70 (1H, m, CH_2CHCH_2), 5.14-5.07 (2H, m, $CH_2CH_2CHCH_2$), 2.41-2.28 (4H, m, $CNCH_2CH_2$). Data consistent to the literature.[155]

Preparation of hex-5-enenitrile 161



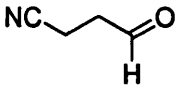
The general procedure for the synthesis is nitrile compounds (**E**) was followed employing 5-bromopentene (1.98 mL, 17 mmol), NaCN (0.92 g, 19 mmol), ethanol (26 mL) and water (7.5 mL). Flash chromatography (1:9 Et_2O: Petrol) yielded the title compound **161** as a colourless oil (1.46 g, 91%); ν_{max} (film)/cm^{-1} 3600, 2950, 1790, 1680, 1410, 977; δ_H (300 MHz; $CDCl_3$) 5.68 (1H, ddt, *J* 17.0, 10.2, 6.7, CH_2CH), 5.05-4.96 (2H, m, $CH_2CH_2CHCH_2$), 2.27 (2H, t, *J* 7.2, $CNCH_2$), 2.17-2.11 (2H, m, CH_2CHCH_2), 1.68 (2H, app. p. *J* 7.2, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 136.3, 119.6, 116.7, 32.4, 23.6, 16.4. Data consistent to the literature.[156]

Preparation of hept-6-enenitrile 162



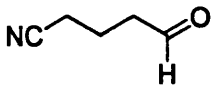
The general procedure for the synthesis of nitrile compounds (**E**) was followed employing 6-chloro-1-hexene (2.2 mL, 16 mmol), NaCN (0.81 g, 17 mmol), ethanol (26 mL) and water (7.5 mL). Flash chromatography (1:9 Et_2O: Petrol) yielded the title compound **162** as a colourless oil (1.65 g, 95%);ν_{max} (film)/cm^{-1} 3532, 3077, 2936, 1833, 1640, 1460, 1427, 914; δ_H (300 MHz; $CDCl_3$) 5.76-5.68 (1H, m, CH_2CH), 5.09-5.02 (2H, m, $CH_2CH_2CHCH_2$), 2.35 (2H, t, *J* 6.9, $CNCH_2$), 2.10 (dt, *J*, 13.8, 6.6, CH_2CHCH_2), 1.72-1.63 (2H, m, $CNCH_2CH_2$), 1.60-1.54 (2H, m, $CNCH_2CH_2CH_2$). Data consistent with the literature.[157]

The general procedure for the ozonolysis of nitrile compounds (F) as exemplified by 4-oxobutanenitrile 163



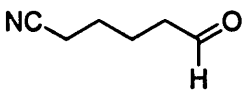
O_3 was bubbled through a solution of pent-4-enenitrile **160** (1.05 g, 12 mmol) in DCM (20 mL) at -78 °C till a colour change to blue was observed. After this time the solution the solution was purged with N_2 till the blue colour had dissipated. Triphenylphosphine (3.8 g, 14 mmol) was added to the resulting solution and the mixture was warmed to room temperature and stirred for one hour. The resulting mixture was reduced *in vacuo* and purified by flash chromatography (1:9 Et_2O: Pentane) to yield the title compound **163** as a colourless oil (0.86g, 85%); ν_{max} (film) /cm^{-1} 3186, 1720, 1420, 913; δ_H (300 MHz; $CDCl_3$) 9.73 (1H, s, C*H*O), 2.85 (2H, t, *J* 7.1, *CH*$_2$CHO), 2.57 (2H, t, *J* 7.1, CN*CH*$_2$); δ_C (75 MHz; $CDCl_3$) 197.5, 118.9, 39.3, 10.4. Data consistent with the literature.[158]

Preparation of 5-oxopentanenitrile 164



The general procedure for the ozonolysis of nitrile compounds (**F**) was followed employing hex-5-enenitrile **161** (1.15 g, 12 mmol), DCM (20 mL) and triphenylphosphine (3.8 g, 14 mmol). Flash chromatography (2:8 Et_2O: Petrol) yielded the title compound **164** as a colourless oil (0.94 g, 81%); ν_{max} (film) /cm^{-1} 2952, 1719, 1416, 1247, 903; δ_H (300 MHz; $CDCl_3$) 9.74 (1H, t, *J* 0.6, C*H*O), 2.63 (2H, td, *J* 7.0, 0.6, *CH*$_2$CHO), 2.39 (2H, t, *J* 7.0, CN*CH*$_2$), 1.91 (app. p, *J*, 7.0, CH$_2$*CH*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 200.6, 119.4, 42.2, 18.3, 16.8. Data consistent with the literature.[159]

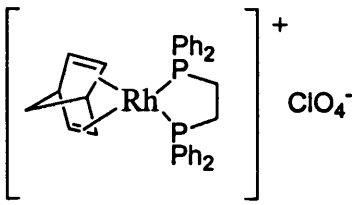
Preparation of 6-oxohexanenitrile 165



The general procedure for the ozonolysis of nitrile compounds (**F**) was followed employing hept-6-enenitrile **162** (0.67 g, 6 mmol), DCM (10 mL) and triphenylphosphine (1.7 g, 7 mmol). Flash chromatography (2:8 Et_2O: Petrol) yielded

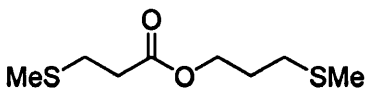
the title compound **165** as a colourless oil (0.55 g, 84%); δ_H (300 MHz; $CDCl_3$) 9.80 (1H, t, *J* 1.4, C*H*O), 2.54 (2H, td, *J* 6.8, 1.4, CH_2CHO), 2.39 (2H, t, *J* 6.8, CNCH_2), 1.80-1.69 (4H, m, $CNCH_2CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 200.9, 119.2, 42.8, 24.8, 21.1, 17.2. Data consistent with the literature.[160]

Preparation of (Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphino)ethane)rhodium (I) perchlorate 168



Norbornadiene rhodium chloride dimer (230 mg, 0.49 mmol) was dissolved in DCM (10 mL). 2,5-Norbornadiene (140 μL, 1.3 mmol) was added, followed by silver perchlorate (270 mg, 1.3 mmol). The mixture was stirred at room temperature for 30 minutes, then 1,2-bis(diphenylphosphino)ethane (350 mg, 0.88 mmol) was added in small portions over 1 minute. The mixture was stirred at room temperature for a further 3 hours then filtered *via* cannula. The solution was evaporated to *ca.* 2 mL then an excess of ethanol was added (approx. 10 mL). The volume of solvent was reduced to induce precipitation which was completed by cooling in an ice bath for 2 hours. The product was recovered by filtration and dried under vacuum to give the title comopund **168** as an orange-red powder (265 mg, 78%); δ_H (300 MHz; $CDCl_3$) 7.58-7.50 (20H, m, Ph), 5.36 (4H, br. s, CH=CH), 4.27 (2H, br. s, CH), 2.40 (4H, d, *J* 20, PCH_2), 1.82 (2H, br. s, CH_2); δ_C (75 MHz; $CDCl_3$) 132.5, 131.8, 129.8, 55.9, 12.8; δ_P (121 MHz, $CDCl_3$) 57.4 (d, *J* 157). Data consistent to that reported in the literature.[23]

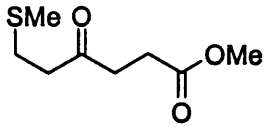
Preparation of 3-(methylthio)propyl 3-(methylthio)propanoate 179



To $Rh(PPh_3)_3Cl$ (7 mg, 0.0075 mmol) in acetone (1.5 mL) 3-methylthioproionaldehyde (15 μL, 0.15 mmol) was added followed by methylacrylate 28 μL, 0.3 mmol. The resulting solution was stirred and heated at 55 °C for 1 hour after which time it was allowed to cool to room temperature and reduced *in vacuo*.

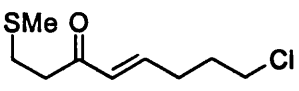
Flash chromatography 2:8 EtOAc: Petrol yield the title compound **179** as a colourless oil (27 mg, 85%); δ_H (300 MHz; $CDCl_3$) 4.14 (2H, t, *J* 6.0, O*CH*$_2$), 2.70 (2H, td, *J* 7.0, 1.5, S*CH*$_2$CH$_2$CO$_2$), 2.56 (2H, td, *J* 7.0, 1.5, SCH$_2$*CH*$_2$CO$_2$), 2.50 (2H, t, *J*, 7.0, *CH*$_2$S), 2.06 (3H, s, S*Me*), 2.04 (3H, s, S*Me*), 1.90-1.85 (2H, m, OCH$_2$*CH*$_2$); δ_C (75 MHz; $CDCl_3$) 170.9, 62.3, 33.4, 29.6, 28.1, 27.1, 14.5, 14.4. Data consistent to the literature.[84]

The general procedure for the use of the new catalyst system (G) as exemplified by methyl 6-(methylthio)-4-oxohexanoate 71



Acetone (1.5 mL) was added under argon to [Rh(COD)Cl]$_2$ (3.7 mg, 0.0075 mmol) followed by silver perchlorate (3.1 mg 0.015 mmol). The resulting mixture was stirred at room temperature for 10 minutes. After this time DPEphos (8 mg, 0.15 mmol) was added and the mixture continued to be stirred for a further 15 minutes. Subsequently 3-(methylthio)propionaldehyde (30 μL, 0.3 mmole) was added immediately followed by methyl acrylate (54 μL, 0.6 mmol). The resulting solution was heated and stirred at 55 °C for 90 minutes. The solution was then cooled to room temperature, reduced *in vacu* and purified by flash chromatography (1:4 EtOAc: Hexane) giving the title compound **71** as a colourless oil (42 mg, 74% yield); δ_H(300 MHz, $CDCl_3$) 3.68 (3H, s, O*Me*), 2.71 - 2.81 (6H, m, MeS*CH*$_2$*CH*$_2$CO*CH*$_2$), 2.61 (2H t, *J* 6.3 Hz, *CH*$_2$CO$_2$Me), 2.11 (3H, s, *Me*S); δ_C(101 MHz, $CDCl_3$) 207.1, 173.2, 51.9, 42.5, 37.3, 27.9, 27.7, 15.79. Data consistent to the literature.[23]

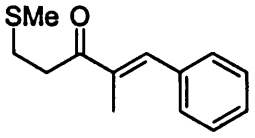
Preparation of *(E)*-8-chloro-2-methanesulfanyl-oct-4-en-3-one 122



The general procedure for the new catalyst system (G) was followed employing [Rh(COD)Cl]$_2$ (3.7 mg, 0.0075 mmol), silver perchlorate (3.1 mg 0.015 mmol), DPEphos (8 mg, 0.15 mmol), 3-(methylthio)propionaldehyde (30 μL, 0.3 mmole) and 5-chloro-1-pentyne (64 μL, 0.6 mmol). Heated at 55 °C for 1 hour. Flash

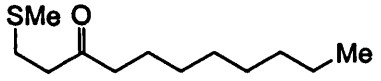
chromatography (1:4 EtOAc: Hexane) yielded the title compound **122** as a yellow oil (50 mg, 82% yield). Data consistent with that reported above.

Preparation of (*E*)-1-methanesulfanyl-4-phenyl-hex-4-en-3-one 151



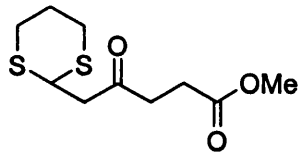
The general procedure for the new catalyst system (**G**) was followed employing $[Rh(COD)Cl]_2$ (3.7 mg, 0.0075 mmol), silver perchlorate (3.1 mg 0.015 mmol), DPEphos (8 mg, 0.15 mmol), 3-(methylthio)propionaldehyde (30 μL, 0.3 mmole) and 1-phenyl-1-propyne (75 μL, 0.6 mmol). Heated at 55 °C overnight. Flash chromatography (1:4 EtOAc: Hexane) yielded the title compound **151** as a yellow oil (53 mg, 80% yield). Data consistent with that reported above.

Preparation of 1-(methylthio)undecan-3-one 190



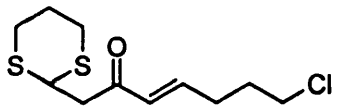
The general procedure for the new catalyst system (**G**) was followed employing $[Rh(COD)Cl]_2$ (3.7 mg, 0.0075 mmol), silver perchlorate (3.1 mg 0.015 mmol), DPEphos (8 mg, 0.15 mmol), 3-(methylthio)propionaldehyde (30 μL, 0.3 mmole) and 1-phenyl-1-propyne (75 μL, 0.6 mmol). Heated at 55 °C overnight. Flash chromatography (1:4 EtOAc: Hexane) yielded the title compound **190** as a yellow oil (44 mg, 69% yield); δ_H (300 MHz; $CDCl_3$) 2.72-2.54 (4H, m, MeSCH_2CH_2), 2.35 (2H, t, *J* 7.5, COCH_2), 2.05 (3H, s, *Me*S), 1.54-1.22 (12H, m, 5 × CH_2), 0.80 (3H, t, *J* 6.1, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 209.8, 43.5, 42.7, 32.2, 29.7, 29.6, 29.5, 28.4, 24.1, 23.0, 16.2, 14.5. Data consistent to that reported in the literature.[23]

Preparation of 5-[1,3]dithian-2-yl-4-oxo-pentanoic acid methyl ester 79



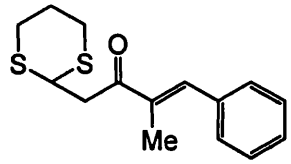
The general procedure for the new catalyst system (**G**) was followed employing [The general procedure for the hydroacylation reaction was followed employing $Rh(COD)Cl]_2$ (3.6 mg, 0.0075 mmol), silver perchlorate (3.0 mg 0.015 mmol), DPEphos (8 mg, 0.015 mmol), 2-(1,3-dithian-2-yl)acetaldehyde (25 mg, 0.15 mmole) and 1-octene (38 μL, 0.30 mmol). Heated at 55 °C for 48 hours. Flash chromatography (1:9 EtOAc: Hexane) yielded the title compound **79** as a yellow oil (31 mg, 72% yield). Data consistent to that reported earlier.

Preparation of (*E*)-7-chloro-1-(1,3-dithian-2-yl)hept-3-en-2-one 112



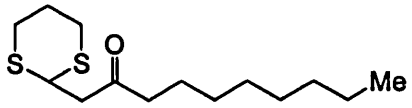
The general procedure for the new catalyst system (**G**) was followed employing [The general procedure for the hydroacylation reaction was followed employing $Rh(COD)Cl]_2$ (1.8 mg, 0.0038 mmol), silver perchlorate (1.5 mg 0.0075 mmol), DPEphos (4 mg, 0.0075 mmol), 2-(1,3-dithian-2-yl)acetaldehyde (25 mg, 0.15 mmole) and 5-chloro-1-pentyne (32 μL, 0.30 mmol). Heated at 55 °C for 4 hours. Flash chromatography (1:9 EtOAc: Hexane) yielded the title compound **112** as a yellow oil (34 mg, 87% yield); ν_{max} (film) /cm^{-1} 2906, 1791, 1463, 1375, 1093, 908, 728; δ_H (300 MHz; $CDCl_3$) 6.79 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.12 (1H, dt, *J* 15.9, 1.5, CO*CH*), 4.48 (1H, t, *J* 7.0, S*CH*), 3.49 (2H, t, *J* 6.4, CH_2Cl), 2.94-2.73 (6H, m, $SCH_2CH_2CH_2SCHCH_2$), 2.39-2.32 (2H, m, $CHCH_2$), 2.11-2.00 (1H, m, SCH_2CHH), 1.94-1.72 (3H, m, SCH_2CHH and CH_2CH_2Cl); δ_C (75 MHz; $CDCl_3$) 195.4, 146.7, 131.1, 45.3, 44.0, 41.7, 30.7, 30.4, 29.6, 25.4; *m/z* (EI+) 264 (15%, $[M]^+$), 201 (20% $[M-CH_2CH_2Cl]^+$), 133 (70% $[M-COCHCHCH_2CH_2CH_2Cl]^+$); found 265.0482 $[M+H]^+$ $C_{11}H_{18}ClOS_2$ requires 265.0482.[125]

Preparation of (*E*)-1-(1,3-dithian-2-yl)-3-methyl-4-phenylbut-3-en-2-one 191



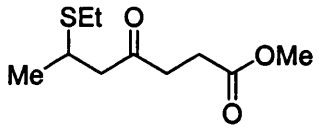
The general procedure for the new catalyst system (**G**) was followed employing [The general procedure for the hydroacylation reaction was followed employing $Rh(COD)Cl]_2$ (1.8 mg, 0.0038 mmol), silver perchlorate (1.5 mg 0.0075 mmol), DPEphos (4 mg, 0.0075 mmol), 2-(1,3-dithian-2-yl)acetaldehyde (25 mg, 0.15 mmole) and 1-phenyl-1-propyne (38 μL, 0.30 mmol). Heated at 55 °C for 24 hours. Flash chromatography (1:9 EtOAc: Hexane) yielded the title compound **191** as a yellow oil (34 mg, 82% yield); ν_{max} (film)/cm^{-1} 2906, 1663, 1211, 908; δ_H (300 MHz; $CDCl_3$) 7.45 (1H, br. s, C*CH*), 7.39-7.24 (5H, m, *Ar*), 4.57 (1H, t, *J* 7.0, S*CH*), 3.14 (2H, d, *J* 7.0, CH*CH*$_2$), 3.00-2.72 (4H, m, S*CH*$_2$CH$_2$*CH*$_2$S), 2.13-2.03 (1H, m, SCH$_2$*CH*H), 2.02 (3H, d, *J* 1.4, *Me*C), 1.88-1.74 (1H, m, SCH$_2$*CH*H); δ_C (75 MHz; $CDCl_3$) 197.6, 139.7, 137.5, 135.6, 129.9, 128.8, 128.5, 42.8, 42.4, 30.4, 25.4, 13.2; *m/z* (EI+) 278 (30%, $[M]^+$), 145 (50% $[M\text{-}SCH_2CH_2CH_2SCHCH_2]^+$); found 279.0871 $[M+H]^+$ $C_{15}H_{19}OS_2$ requires 279.0872.[125]

Preparation of 1-(1,3-dithian-2-yl)decan-2-one 192



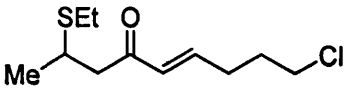
The general procedure for the new catalyst system (**G**) was followed employing [The general procedure for the hydroacylation reaction was followed employing $Rh(COD)Cl]_2$ (3.6 mg, 0.0075 mmol), silver perchlorate (3.0 mg 0.015 mmol), DPEphos (8 mg, 0.015 mmol), 2-(1,3-dithian-2-yl)acetaldehyde (25 mg, 0.15 mmole) and 1-octene (38 μL, 0.30 mmol). Heated at 55 °C for 48 hours. Flash chromatography (1:9 EtOAc: Hexane) yielded the title compound **192** as a yellow oil (34 mg, 82% yield); ν_{max} (film)/cm^{-1} 2906, 1663, 1211, 908; δ_H (300 MHz; $CDCl_3$) 3.80 (1H, t, *J* 6.8, S*CH*), 3.15 (2H, d, *J* 6.8, CH*CH*$_2$), 2.52-2.18 (6H, m, S*CH*$_2$CH$_2$*CH*$_2$S and CO*CH*$_2$), 1.99-1.24 (14H, m, 7 × *CH*$_2$), 0.95 (3H, t, *J* 7.0, CH$_2$*CH*$_3$). Data consistent with the literature.[161]

Preparation of methyl 6-(ethylthio)-4-oxoheptanoate 106



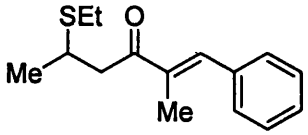
The general procedure for the new catalyst system (**G**) was followed employing $[Rh(COD)Cl]_2$ (1.8 mg, 0.0038 mmol), silver perchlorate (1.5 mg 0.0075 mmol), DPEphos (4 mg, 0.0075 mmol), 3-(ethylthio)butanal (20 μL, 0.15 mmole) and methyl acrylate (27 μL, 0.30 mmol). Heated at 55 °C overnight. Flash chromatography (1:4 EtOAc: Hexane) yielded the title compound **106** as a yellow oil (26 mg, 81% yield). Data consistant to that reported above.

Preparation of *(E)*-9-chloro-2-(ethylthio)non-5-en-4-one 193



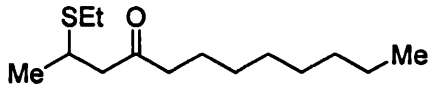
The general procedure for the new catalyst system (**G**) was followed employing $[Rh(COD)Cl]_2$ (1.8 mg, 0.0038 mmol), silver perchlorate (1.5 mg 0.0075 mmol), DPEphos (4 mg, 0.0075 mmol), 3-(ethylthio)butanal (20 μL, 0.15 mmole) and 5-chloro-1-pentyne (32 μL, 0.30 mmol). Heated at 55 °C overnight. Flash chromatography (1:4 EtOAc: Hexane) yielded the title compound **193** as a yellow oil (34 mg, 97% yield);); ν_{max} (film)/cm^{-1} 3039, 1668, 1416, 1267, 744; δ_H (300 MHz; $CDCl_3$) 6.75 (1H, dt, *J* 15.9, 6.9, COCH*CH*), 6.10 (1H, dt, *J* 15.9, 1.5, CO*CH*), 3.49 (2H, t, *J* 6.4, CH_2Cl), 3.32-3.20 (1H, m, Me*CH*), 2.79 (1H, dd, *J* 16.3, 5.6, *CH*HCO), 2.60 (1H, dd, *J* 16.3, 8.3, *CH*HCO), 2.51 (2H, q, *J* 7.4, CH_3CH_2S), 2.38-2.30 (2H, m, $CHCH_2$), 1.93-1.84 (2H, m, CH_2CH_2Cl), 1.23 (3H, d, *J* 6.7, *Me*CH), 1.19 (3H, t, *J* 7,4, CH_3CH_2S); δ_C (75 MHz; $CDCl_3$) 197.9, 145.4, 131.1, 47.4, 43.8, 34.7, 30.5, 29.3, 24.6, 21.4, 14.5; *m/z* (EI+) 234 (10%, $[M]^+$), 172 (20% $[M\text{-}EtSH]^+$), 131 (100% $[M\text{-}EtSCH(CH_3)CH_2]^+$); found 235.0918 $[M+H]^+$ $C_{11}H_{20}ClOS$ requires 235.0918; Anal. Calc. for $C_{11}H_{19}ClOS$: C, 56.27, H, 8.16. Found C, 56.7, H, 8.14%.[125]

Preparation of *(E)*-5-(ethylthio)-2-methyl-1-phenylhex-1-en-3-one 194



The general procedure for the new catalyst system (**G**) was followed employing $Rh(COD)Cl]_2$ (1.8 mg, 0.0038 mmol), silver perchlorate (1.5 mg 0.0075 mmol), DPEphos (4 mg, 0.0075 mmol), 3-(ethylthio)butanal (20 μL, 0.15 mmole) and 1-phenyl-1-propyne (38 μL, 0.30 mmol). Heated at 55 °C for 30 hours. Flash chromatography (1:4 EtOAc: Hexane) yielded the title compound **194** as a yellow oil (27 mg, 73% yield); ν_{max} (film)/cm^{-1} 2980, 1796, 1663, 1473, 908; δ_H (300 MHz; $CDCl_3$) 7.45 (1H, br. s, C*CH*), 3.41-3.30 (1H, m, Me*CH*), 3.06 (1H, dd, *J* 16.4, 5.4, *CH*HCO), 2.87 (1H, dd, *J* 16.4, 8.4, *CH*HCO), 2.54 (2H, q, *J* 7.4, CH_3CH_2S), 2.01 (3H, d, *J* 1.3, *Me*C), 1.27 (3H, d, *J* 6.7, *Me*CH), 1.21 (3H, t, *J* 7.4, CH_3CH_2S); δ_C (75 MHz; $CDCl_3$) 200.7, 139.5, 138.0, 136.2, 124.4, 45.5, 36.0, 25.3, 22.1, 15.2, 13.6; *m/z* (EI+) 248 (2%, $[M]^+$), 186 (40% $[M\text{-}EtSH]^+$), 115 (100% $[M\text{-}PhCHC(CH_3)O]^+$); found 249.1309 $[M+H]^+$ $C_{15}H_{21}OS$ requires 249.1308.[125]

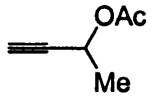
Preparation of 2-(ethylthio)dodecan-4-one 195



The general procedure for the new catalyst system (**G**) was followed employing $[Rh(COD)Cl]_2$ (1.8 mg, 0.0038 mmol), silver perchlorate (1.5 mg, 0.0075 mmol), DPEphos (4 mg, 0.0075 mmol), 3-(ethylthio)butanal (20 μL, 0.15 mmole) and 1-octene (47 μL, 0.3 mmol). Heated at 55 °C for 48 hours. Flash chromatography (1:9 EtOAc: Hexane) yielded the title compound **195** as a yellow oil (22 mg, 51% yield); ν_{max} (film)/cm^{-1} 2980, 1796, 1663, 1473, 908; δ_H (300 MHz; $CDCl_3$) 3.27-3.16 (1H, m, Me*CH*), 2.87-2.75 (1H, m, *CH*HCO), 2.64 (1H, dd, *J* 16.7, 5.9, *CH*HCO), 2.55-2.31 (4H, m, CH_3CH_2S and $COCH_2CH_2$), 1.61-1.45 (2H, m, $COCH_2CH_2$), 1.25-1.16 (14H, m, CH_3CH_2SCHMe and 4 × CH_2), 0.81 (3H, t, *J* 6.8, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 209.7, 50.4, 44.1, 35.1, 32.2, 29.8, 29.6, 29.5, 25.1, 24.1, 23.1, 22.1, 15.2, 14.5; *m/z* (CI+, NH_3) 262 (60%, $[M+NH_3]^+$), 245 (50% $[M+H]^+$), 200 (100% [M-

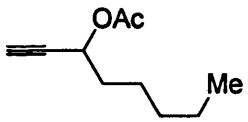
EtMe]$^+$), 183 (40%, [M-SEt]$^+$); found 245.1934 [M+H]$^+$ $C_{14}H_{29}OS$ requires 245.1935.[125]

The general procedure for the acetylation of alcohols (H) as exemplified by but-3-yn-2-yl acetate 205



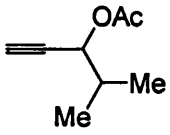
To 3-butyn-2-ol (2.00 g, 28.5 mmol) in pyridine (25 mL) at room temperature DMAP (340 mg, 2.8 mmol) was added followed by acetic anhydride (2.70 mL, 28.5 mmol). The reaction was stirred at room temperature for 4 hours after which NH_4Cl (aq) (20 mL) and Et_2O (100 mL) were added. The resulting mixture separated and the organic extract was washed with 1M HCl (3 × 100 mL). The organic layer was dried with $MgSO_4$, reduced *in vacu* and purified by flash chromatography (2:8 Et_2O: hexane) to yield the title compound **205** as a yellow oil (2.62 g, 82%). ν_{max} (film)/cm^{-1} 3008, 2366, 1735, 1375, 1242; δ_H (300 MHz; $CDCl_3$) 5.35 (1H, qd, *J* 6.7, 2.1, CHC*CH*CH$_3$), 2.40 (1H, d, *J* 2.1, *CH*CCHCH$_3$), 2.01 (3H, s, OCO*CH$_3$*), 1.43 (3H, d, *J* 6.7, CHCCH*CH$_3$*); δ_C(75 MHz; $CDCl_3$) 169.4, 81.8, 72.6, 59.7, 20.9, 20.7. Data consistent with the literature.[162]

Preparation of oct-1-yn-2-yl acetate 206



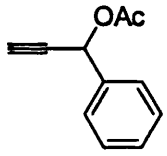
The general procedure for the acetylation of alcohols (**H**) was followed employing. 1-octyn-3-ol (4.16 mL, 28.5 mmol), pyridine (25 mL), DMAP (340 mg, 2.8 mmol) and acetic anhydride (2.70 mL, 28.5 mmol). Reaction stirred for 4 hours at room temperature. Flash chromatography (2:8 Et_2O: hexane) yielded the title compound **206** as a pale yellow oil (3.51 g, 78%). δ_H (300 MHz; $CDCl_3$) 5.32 (1H, td, *J* 6.7, 2.1, CHC*CH*OAc), 2.43 (1H, d, *J* 2.1, *CH*CCHOAc), 2.07 (3H, s, OCO*CH$_3$*), 1.78-1.71 (2H, m, OAcCH*CH$_2$*CH$_2$), 1.50-1.35 (2H, m, CHCH$_2$CH$_2$CH$_2$*CH$_2$*CH$_3$), 1.36-1.24 (4H, m, CHCH$_2$*CH$_2$CH$_2$*CH$_2$CH$_3$), 0.88 (3H, t, *J* 6.9, CHCH$_2$CH$_2$CH$_2$CH$_2$*CH$_3$*); δ_C (75 MHz; $CDCl_3$) 169.8, 81.3, 73.3, 63.7, 34.5, 31.2, 24.5, 22.4, 20.9, 13.9. Data consistent with the literature.[163]

Preparation of 4-methylpent-1-yn-3-yl acetate 207



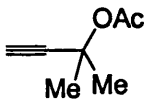
The general procedure for the acetylation of alcohols (**H**) was followed employing. 4-methyl-1-pentyn-3-ol (3.00 g, 30 mmol), pyridine (25 mL), DMAP (370 g, 3 mmol) and acetic anhydride (2.90 mL, 30 mmol). Reaction stirred overnight at room temperature. Flash chromatography (2:8 Et_2O: hexane) yielded the title compound **207** as a pale yellow oil (3.15 g, 75%). ν_{max} (film)/cm^{-1} 3291, 2972, 1740, 1478, 1226; δ_H (300 MHz; $CDCl_3$) 5.18-5.07 (1H, m,C*CH*OAc), 2.38 (1H, d, *J* 2.1, *CH*CCH), 2.02 (3H, d, *J* 1.3, OCO*CH*$_3$), 1.93 (1H, qd, 12.6, 6.5, CHC*H*$(CH_3)_2$), 1.02-0.89 (6H, m, CHC*H*$(CH_3)_2$); δ_C (75 MHz; $CDCl_3$) 170.2, 80.2, 74.4, 69.0, 32.5, 18.4, 17.7. Data consistent with the literature.[164]

Preparation of 1-phenylprop-2-ynyl acetate 208



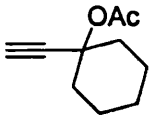
The general procedure for the acetylation of alcohols (**H**) was followed employing. 1-phenyl-2-propyn-1-ol (1.00 g, 7.6 mmol), pyridine (8 mL), DMAP (90 mg, 0.76 mmol) and acetic anhydride (0.72 mL, 7.6 mmol). Reaction was stirred at room temperature for 16 hours. Flash chromatography (2:8 Et_2O: hexane) yielded the title compound **208** as a yellow oil (1.04 g, 79%). ν_{max} (film)/cm^{-1} 3275, 1745, 1457, 1221, 1021; δ_H (300 MHz; $CDCl_3$) 7.50-7.43 (2H, m, Ar), 7.39-7.27 (3H, m, Ar), 6.39 (1H, d, *J* 2.4, CHC*CH*Ph), 2.60 (1H, d, *J* 2.4, *CH*CCH), 2.05 (3H, s, OCO*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 170.1, 136.8, 129.5, 129.1, 128.1, 80.6, 75.8, 65.7, 21.5; Data consistent with the literature.[165]

Preparation of 2-methylbut-3-yn-2-yl acetate 209



The general procedure for the acetylation of alcohols (**H**) was followed employing: 2-methyl-3-butyn-2-ol (3.2 mL, 33 mmol), pyridine (30 mL), DMAP (400 mg, 3.3 mmol) and acetic anhydride (3.1 mL, 33 mmol). Reaction stirred for 16 hours at room temperature. Flash chromatography (1:4 Et_2O: hexane) yielded the title compound **209** as a pale yellow oil (2.49 g, 84%). ν_{max} (film)/cm^{-1}3296, 2988, 1735, 1366, 1247; δ_H (300 MHz; $CDCl_3$) 2.49 (1H, s, *CH*CCOAc), 1.98 (3H, s, OCO*CH*$_3$), 1.62 (6H, s, CHCC*(CH*$_3$*)*$_2$); δ_C (75 MHz; $CDCl_3$) 169.2, 84.6, 72.1, 71.4, 28.8, 21.8. Data consistent with the literature.[166]

Preparation of 1-cyclohexylprop-2-ynyl acetate 210

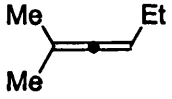


The general procedure for the acetylation of alcohols (**H**) was followed employing. 1-ethynyl-1-cyclohexanol (3.50 g, 28 mmol), pyridine (20 mL), DMAP (340 mg, 2.8 mmol) and acetic anhydride (2.70 mL, 28 mmol). Reaction stirred for 16 hours at room temperature. Flash chromatography (2:8 Et_2O: pentane) yielded the title compound **210** as a yellow oil (3.6g, 78%). ν_{max} (film)/cm^{-1} 3291, 2936, 1750, 1452, 1237; δ_H (300 MHz; $CDCl_3$) 2.53 (1H, s, *CH*C), 2.09-2.01 (2H, m, CC*CH*$_2$), 1.97 (3H, s, CO*CH*$_3$), 1.82-1.73 (2H, m, CC*CH*$_2$), 1.59-1.39 (6H, m, CCCH$_2$*CH*$_2$*CH*$_2$*CH*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 169.7, 84.0, 74.6, 66.2, 37.3, 25.5, 22.8, 22.3. Data consistent with the literature.[167]

The general procedure for the synthesis of allenes (I) as exemplified by nona-2,3-diene 211

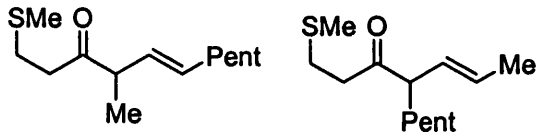
To But-3-yn-2-yl acetate **205** (1.00 g, 8.9 mmol) in Et_2O (40 mL), CuBr (130 mg, 0.89 mmol) was added. The resulting mixture was stirred and cooled to –78 °C for 30 minutes. After this time PentMgBr (2 M in Et_2O) (4.90 mL, 9.8 mmol) was added in one portion. The reaction was then allowed to stir for 1 hour at -78 °C after which it was warmed to room temperature and further stirred for 1 hour. After this time the reaction was hydrolysed with 1:4 NH_3 (aq): NH_4Cl (aq) (100 mL) and separated. The organic phase was dried ($MgSO_4$) and purified using flash chromatography (pentane) to yield the title compound **211** as a clear oil (0.57 g, 52%). ν_{max} (film)/cm^{-1} 2926, 2854, 1463; δ_H (300 MHz; $CDCl_3$) 5.12-5.01 (2H, m, *CHCCH*), 2.03-1.91 (2H, m, CCH*CH*$_2$), 1.36-1.23 (9H, m, CH*CH*$_3$ and CH_2*CH*$_2$*CH*$_2$*CH*$_2$), 0.91-0.23 (3H, m, CH_2*CH*$_3$); δ_C (75 MHz; $CDCl_3$); 203.8, 90.9, 84.7, 31.9, 29.7, 29.0, 22.5, 16.1, 14.1. Data consistent with the literature.[168]

Preparation of 2-methylhexa-2,3-diene 212



The general procedure for the synthesis of allenes (**I**) was followed employing: 2-methylbut-3-yn-2-yl acetate **209** (1.00 g, 7.9 mmol), Et_2O (50 mL), CuBr (110 mg, 0.79 mmol) and EtMgBr (2M in Et_2O) (4.30 mL, 8.7 mmol). Flash chromatography yielded the title compound **212** as a colourless oil (0.37g, 49%). ν_{max} (film)/cm^{-1} 2926, 2844, 1452; δ_H (300 MHz; $CDCl_3$) 5.00-4.86 (1H, m, CC*CH*), 1.94-1.83 (2H, m, *CH*$_2$CH$_3$), 1.62 (3H, s, C*CH*$_3$), 1.60 (3H, s, C*CH*$_3$), 0.91 (3H, t, *J* 7.4, CH_2*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 202.1, 95.1, 89.2, 23.1, 21.2, 14.5. Data consistent with the literature.[169]

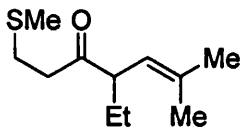
Preparation of (*E*)-4-methyl-1-(methylthio)undec-5-en-3-one 213a and (*E*)-1-(methylthio)-4-(prop-1-enyl)nonan-3-one 213b



213a **213b**

The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and nona-2,3-diene **211** (37 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compounds **213a** and **213b** (1:1.25) as a yellow oil (1:1.25, **213a:213b**, 33 mg, 97%); ν_{max} (film)/cm^{-1} 3049, 1647, 1421, 1262; δ_H (300 MHz; $CDCl_3$) (**213a**) 5.58-5.46 (1H, m, CH*CH*CH_2), 5.28 (1H, ddt, *J* 16.5, 8.3, 1.4, CH*CH*CH), 3.12-3.03 (1H, m, CH_3*CH*), 2.79-2.56 (4H, m, MeS*CH_2CH_2*), 2.16-1.92 (3H, m, *Me*S), 1.36-1.13 (8H, m , *$CH_2CH_2CH_2CH_2$*CH_3), 1.08 (3H, d, *J* 6.9, *CH_3*CH), 0.83-0.78 (3H, m, CH_2*CH_3*); δ_H (300 MHz; $CDCl_3$) (**213b**) 5.58-5.46 (1H, m, CH*CH*CH_2), 5.25 (1H, ddq, *J* 16.5, 9.0, 1.5, CH*CH*CH), 3.12-3.03 (1H, m, CH_3*CH*), 2.79-2.56 (4H, m, MeS*CH_2CH_2*), 2.16-1.92 (3H, m, *Me*S), 1.62 (3H, dd, *J* 6.4, 1.5), 1.36-1.13 (8H, m , *$CH_2CH_2CH_2CH_2$*CH_3), 0.83-0.78 (3H, m, CH_2*CH_3*); δ_C (75 MHz; $CDCl_3$) (both) 207.2, 206.3, 134.4, 129.5, 129.3, 129.1, 57.2, 51.0, 41.3, 40.6, 32.9, 32.1, 32.0, 29.6, 29.5, 29.2, 28.4, 27.5, 23.1, 23.0, 18.4, 16.5, 16.3, 16.2, 14.5, 14.4; *m/z* (EI+) 228 (20%, $[M]^+$), 102 (75%, $[M\text{-}CH_3CHCHCHCH_2CH_2CH_2CH_2CH_3]^+$), 75 (100%, $[M\text{-}\ CH_3CHCHCHCH_2CH_2CH_2CH_2CH_3CO]^+$); found $[M+H]^+$ 229.1621, $C_{13}H_{25}OS$ requires 229.1621.

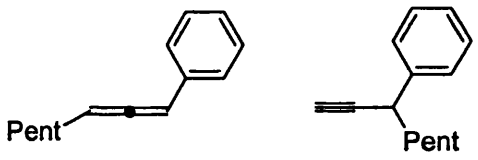
Preparation of 4-ethyl-6-methyl-1-(methylthio)hept-5-en-3-one 214



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-

methylthiol propionaldehyde (15 μL, 0.15 mmol) and 2-methylhexa-2,3-diene **212** (29 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **214** as a yellow oil (24 mg, 80%); ν_{max} (film)/cm^{-1} 3020, 1747, 1457, 1142; δ_H (300 MHz; $CDCl_3$) 4.91-4.82 (1H, m, *CH*C$(CH_3)_2$), 3.23-3.15 (1H, m, *CH*CHC), 2.71-2.57 (4H, m, MeS*CH₂CH₂*), 2.03 (3H, s, *Me*S), 1.65 (6H, dd, *J* 13.9, 1.3, C(*CH₃*)₂), 1.32-1.05 (2H, m, CH_3CH_2), 0.80 (3H, t, *J* 6.7, *CH₃*CH_2); δ_C (75 MHz; $CDCl_3$) 210.6, 136.1, 123.2, 53.1, 41.1, 32.1, 26.3, 23.0, 18.8, 14.5; *m/z* (EI+) 200 (2% $[M]^+$) 97 (30%, $[M\text{-}MeSCH_2CH_2CO]^+$), 55 (100%, $[M\text{-}MeSCH_2CH_2COCHCH_2CH_3]^+$); found $[M+H]^+$ 201.1306, $C_{11}H_{21}OS$ requires 201.1308.

Preparation of 1-(octa-1,2-dienyl)benzene 216 and 1-(oct-1-yn-3-yl)benzene 217



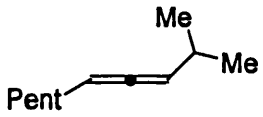
216 **217**

The general procedure for the synthesis of allenes (**I**) was followed employing: Oct-1-yn-2-yl acetate **206** (1.00 g, 5.9 mmol), Et_2O (30 mL), CuBr (90 mg, 0.6 mmol) and PhMgBr (3 M in diethyl ether) (2.20 mL, 6.5 mmol). Flash chromatography yielded 1-(octa-1,2-dienyl)benzene **216** as a colourless oil (0.76 g, 70%); ν_{max} (film)/cm^{-1} 2921, 1950, 1653; δ_H (300 MHz; $CDCl_3$) 7.29-7.14 (5H, m), 6.12 (1H, dt, *J* 6.2, 3.0), 5.56 (1H, app. q, 6.8), 2.12 (2H, dtd, *J* 7.9, 6.9, 3.0), 1.53-1.44 (2H, m), 1.35-1.26 (4H, m), 0.88 (3H, t, *J* 6.7); δ_C (75 MHz; $CDCl_3$) 205.2, 135.6, 128.9, 127.0, 126.9, 97.2, 95.6, 34.5, 22.8, 22.4, 14.5, 13.9. Data consistent with the literature,[145] and 1-(oct-1-yn-3-yl)benzene **217** as a colourless oil (0.11 g, 10%); δ_H (300 MHz; $CDCl_3$) 7.38-7.12 (5H, m, Ar), 3.53 (1H, td, *J* 6.6, 2.5, Ph*CH*), 2.17 (1H, d, *J* 2.5, *CH*CCH), 1.71-1.62 (2H, m, CH*CH₂*), 1.45-1.15 (6H, m, $CHCH_2CH_2CH_2CH_2$), 0.79 (3H, t, *J* 7.6 CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 142.2, 129.2, 128.9, 127.8, 86.6, 71.2, 38.7, 38.0, 31.9, 27.4, 22.9, 14.5. Data consistent with the literature.[170]

Preparation of trideac-6,7-diene 218

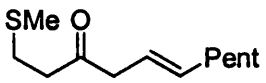
The general procedure for the synthesis of allenes (**I**) was followed employing: Oct-1-yn-2-yl acetate **206** (1.00 g, 6.0 mmol), Et_2O (30 mL), CuBr (86 mg, 0.6 mmol) and PentMgBr (2M in diethyl ether) (3.30 mL, 6.6 mmol). Flash chromatography yielded the title compound **218** as a colourless oil (6.4 g, 59%). ν_{max} (film)/cm^{-1} 2942, 1956, 1468, 1355; δ_H (300 MHz; $CDCl_3$) 5.09-5.03 (2H, m, *CHCCH*), 2.01-1.93 (4H, m, 2 × $CH\mathit{CH_2}$), 1.32-1.26 (12 H, m, 2 × $CHCH_2(\mathit{CH_2})_3CH_3$), 0.89 (3H, t, *J* 6.8, $CH_2\mathit{CH_3}$), 0.88 (3H, t, *J* 6.7, $CH_2\mathit{CH_3}$); δ_C (75 MHz; $CDCl_3$) 203.8, 90.9, 31.9, 29.4, 28.9, 22.4, 14.1. Data consistent with the literature.[140]

Preparation of 2-methyldeca-3,4-diene 219



The general procedure for the synthesis of allenes (**I**) was followed employing: 2-methylbut-3-yn-2-yl acetate **207** (1.00 g, 7.9 mmol), Et_2O (40 mL), CuBr (110 mg, 0.79 mmol) and PhMgBr (3 M in diethyl ether) (2.91 mL, 8.7 mmol). Flash chromatography yielded the title compound **219** as a colourless oil (0.7g, 64%). ν_{max} (film)/cm^{-1} 2962, 2361, 1452; δ_H (300 MHz; $CDCl_3$) 5.09-4.98 (2H, m, *CHCCH*), 2.25-2.13 (1H, m, $CH\mathit{CH}(CH_3)_2$), 1.95-1.86 (2H, m, $CH\mathit{CH_2}CH_2$), 1.38-1.11 (6H, m, $CH_3\mathit{CH_2CH_2CH_2}$), 0.94 (6H, d, *J* 6.7, $CH(CH_3)_2$), 0.81 (3H, t, *J* 6.7, $\mathit{CH_3}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 202.6, 98.8, 92.6, 34.5, 32.3, 30.1, 29.3, 28.4, 22.9, 22.7, 14.5.

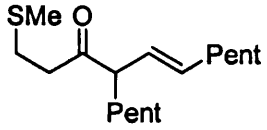
Preparation of *(E)*-1-(methylthio) undec-5-en-3-one 220



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and octa-1,2-diene **215** (33 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography 9:1 Hexane: EtOAc)

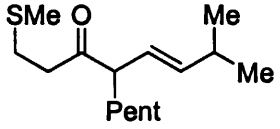
yielded the title compound **220** as a pale yellow oil (26 mg, 87%); υ_{max} (film) / cm^{-1} 2955, 2927, 2858, 1715; δ_H(300 MHz, $CDCl_3$) 5.65- 5.45 (2H, m, C*H*=C*H*), 3.11 (2H, d, *J* 5.2, CH_2CH=CH), 2.73 (4H, br t, *J* 6.8, CH_2CH_2S), 2.12 (3H, br s, SMe), 2.02 (2H, q, *J* 6.7, CH_2CH_3), 1.40-1.20 (6H, m, $CH_2CH_2CH_2$), 0.88 (3H, t, *J* 6.7, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 208.1, 134.6, 120.8, 47.4, 42.1, 32.9, 31.7, 29.2, 28.2, 22.9, 16.1,14.4.; *m/z* (CI+, NH_3) 232 (100 %, $[M+NH_4]^+$), 215 (20%, $[M+H]^+$, 200 (30%, $[M-CH_2]^+$, 184 (70%, $[M-CH_3CH_3]^+$; found 232.1730 $[M+NH_4]^+$ $C_{12}H_{26}NOS_2$ requires 232.1730.

Preparation of *(E)*-1-(methylthio)-4-pentylundec-5-en-3-one 221



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and trideac-6,7-diene **218** (54 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **221** as a yellow oil (30 mg, 70%); ν_{max} (film)/cm^{-1} 2926, 1699, 1457, 898, 718; δ_H (300 MHz; $CDCl_3$) 5.58 (1H, dt, *J* 15.4, 6.8), 5.26 (1H, ddt, *J* 15.4, 9.1, 1.6), 3.01 (1H, dt, *J* 9.1, 7.0), 2.85-2.64 (4H, m), 2.10 (3H, s), 2.06-1.97 (2H, m), 1.78-1.62 (2H, m), 1.43-1.19 (12H, m), 0.94-0.83 (6H, m); δ_C (75 MHz; $CDCl_3$) 2210.2, 134.9, 127.7, 56.9, 40.9, 32.5, 31.7, 31.6, 31.3, 30.9, 28.9, 28.0, 26.8, 22.5, 15.8, 14.1, 14.0; *m/z* (EI+) 284 (3% $[M]^+$), 103 (100%, [M-PentCHCHCHPent]$^+$); found $[M+H]^+$ 285.2247, $C_{17}H_{33}OS$ requires 285.2247.

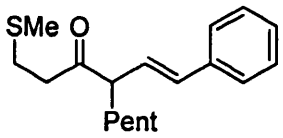
Preparation of (E)-4-(3-methylbut-1-enyl)-1-methylthio)nonan-3-one 222



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 2-methyldeca-3,4-diene **219** (46 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:9,

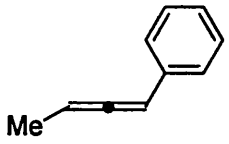
Et_2O:Hexane) yielded the title compound **222** as a yellow oil (35 mg, 92%); ν_{max} (film)/cm^{-1} 2916, 1704, 1463, 903; δ_H (300 MHz; $CDCl_3$) 5.48 (1H, dd, *J* 15.4, 6.7, CH*CH*CHCH$(CH_3)_2$), 5.15 (1H, ddd, *J* 15.4, 9.0, 1.2, CHCH*CH*CH$(CH_3)_2$), 2.92 (1H, m, CO*CH*CH), 2.77-2.55 (4H, m, MeSCH_2CH_2), 2.29-2.16 (1H, m, CHCHCH*CH*$(CH_3)_2$), 2.03 (3H, s, *Me*S), 1.70-1.56 (1H, m, COCHCH_aH_b), 1.41-1.30 (1H, m, COCHCH_aH_b), 1.27-1.09 (6H, m, $CHCH_2CH_2CH_2CH_2CH_3$), 0.92 (3H, d, *J* 1.2, CH(*CH*$_3$)CH_3), 0.90 (3H, d, *J* 1.2, CH$(CH_3)CH_3$), 0.82-0.77 (3H, m, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 210.6, 142.1, 125.2, 57.2, 41.3, 32.1, 32.0, 31.6, 31.3, 28.4, 27.2, 22.9, 22.7, 16.2, 14.4; *m/z* (EI+) 256 (10% $[M]^+$), 103 (60%, [M-$Me_2CHCHCH(CH_2)_4CH_3]^+$), 75 (100%, [M-$Me_2CHCHCH(CH_2)_4CH_3CO]^+$); found $[M+H]^+$ 257.1931, $C_{15}H_{29}S$ requires 257.1934.

Preparation of (E)-1-(methylthio)-4-styrylnonan-3-one 223



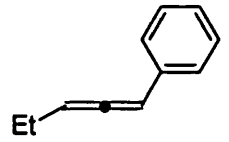
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(octa-1,2-dienyl)benzene **216** (56 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **223** as a yellow oil (39 mg, 89%); ν_{max} (film)/cm^{-1} 2926, 1709, 1457, 908; δ_H (300 MHz; $CDCl_3$) 7.32-7.14 (5H, m, Ar), 6.43 (1H, d, *J* 15.8, CH*CH*Ph), 6.0 (1H, dd, *J* 15.8, 9.3, *CH*CHPh), 3.17 (1H, dt, *J* 9.3, 6.8, CO*CH*CH), 2.83-2.62 (4H, m, MeSCH_2CH_2CO), 2.02 (3H, s, *Me*S), 1.78-1.68 (1H, m, COCHCH_aH_b), 1.55-1.45 (1H, m, COCHCH_aH_b), 1.27-1.16 (6H, m, $CHCH_2CH_2CH_2CH_2CH_3$), 0.82-0.67 (3H, m, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 209.8, 137.1, 133.6, 129.0, 128.1, 128.0, 126.7, 57.6, 41.8, 32.1, 31.6, 28.4, 27.3, 22.9, 16.2, 14.4; *m/z* (EI+) 290 (20% $[M]^+$), 187 (40%, [M-$MeSCH_2CH_2CO]^+$), 116 (100%, [M-$PhCHCHCH_2CH_2CH_2CH_2CH_3]^+$); found $[M+H]^+$ 291.1783, $C_{18}H_{27}OS$ requires 291.1777.

Preparation of 1-(buta-1,2-dienyl)benzene 224



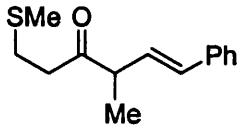
The general procedure for the synthesis of allenes (**I**) was followed employing: But-3-yn-2-yl acetate **205** (1.00 g, 8.9 mmol), Et_2O (60 mL), CuBr (130 mg, 0.89 mmol), PhMgBr (3 M in diethyl ether) (3.32 mL, 9.8 mmol). Flash chromatography yielded the title compound **224** as a colourless oil (0.72 g, 62%); ν_{max} (film) /cm^{-1} 3049, 2983, 1409, 1267; δ_H (300 MHz; $CDCl_3$) 7.24-7.19 (4H, m, *Ar-H*), 7.15-7.05 (1H, m, *Ar-H*), 6.01 (1H, dq, *J* 6.4, 3.1, MeCH*CH*Ph), 5.45 (1H, qd, *J* 7.0, 6.4 Me*CH*CH), 1.71 (3H, dd, *J* 7.0, 3.1, *Me*CHCH); δ_C (75 MHz; $CDCl_3$) 206.4, 135.5, 128.9, 127.0, 94.4, 89.9, 14.5. Data consistent with the literature.[167]

Preparation of 1-(penta-1,2-dienyl)benzene 225



The general procedure for the synthesis of allenes (**I**) was followed employing: 1-phenylprop-2-ynyl acetate **208** (1.00 g, 6.0 mmol), Et_2O (30 mL), CuBr (86 mg, 0.6 mmol) and PentMgBr (2 M in diethyl ether) (3.32 mL, 6.6 mmol). Flash chromatography yielded the title compound **225** as a colourless oil (0.56 g, 65%). δ_H (300 MHz; $CDCl_3$) 7.27-7.09 (5H, m, *Ar-H*), 6.10-6.07 (1H, m, *CH*Ph), 5.59-5.53 (1H, m, CH_2CH), 2.13-2.02 (2H, CH_3CH_2), 1.00 (3H, t, *J* 7.6, CH_3CH_2); δ_C (75 MHz; $CDCl_3$) 205.2, 135.6, 128.9, 127.0, 126.9, 97.2, 95.6, 22.8, 13.9. Data consistent with the literature.[171]

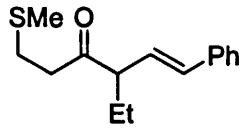
Preparation of *(E)*-4-methyl-1-(methylthio)-6-phenylhex-5-en-3-one 226



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(buta-1,2-dienyl)benzene **224**

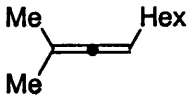
(39 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **226** as a yellow oil. (34 mg, 97%); ν_{max} (film) /cm^{-1} 2972, 1709, 1447, 898; δ_H (300 MHz; $CDCl_3$) 7.31-7.14 (5H, m, *Ar*), 6.42 (1H, d, *J* 15.8, *CH*Ph), 6.08 (1H, dd, *J* 15.8, 8.3, *CH*CHPh), 3.36-3.25 (1H, m, Me*CH*), 2.87-2.63 (4H, m, MeSCH_2CH_2), 2.02 (3H, s, *Me*S), 1.21 (3H, d, *J* 6.8, *Me*CH); δ_C (75 MHz; $CDCl_3$) 209.9, 137.1, 132.8, 129.0, 128.9, 128.2, 126.6, 51.3, 41.0, 28.4, 16.5, 16.2; *m/z* (EI+) 234 (30% $[M]^+$), 130 (10%, $[M-MeSCH_2CH_2COH]^+$), 91 (80%, $[M-PhCHCHCHMeO]^+$); found $[M+H]^+$ 235.1152, $C_{14}H_{19}OS$ requires 235.1151.

Preparation of *(E)*-4-ethyl-1-(methylthio)-6-phenylhex-5-en-3-one 227



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(penta-1,2-dienyl)benzene **225** (43 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **227** as a yellow oil (33 mg, 89%); ν_{max} (film)/cm^{-1} 2989, 1723, 1406, 917; δ_H (300 MHz; $CDCl_3$) 7.31-7.12 (5H, m, Ph), 6.44 (1H, d, *J* 15.8, CH*CH*Ph), 6.00 (1H, dd, *J* 15.8, 9.3, *CH*CHPh), 3.13-3.05 (1H, m, CO*CH*CH), 2.83-2.56 (4H, m, MeSCH_2CH_2), 2.03 (3H, s, MeS), 1.87-1.73 (1H, m, $CH CH_aH_bCH_3$), 1.60-1.46 (1H, m, $CHCH_aH_bCH_3$), 0.84 (3H, t, *J* 7.4, CH_3CH_2); δ_C (75 MHz; $CDCl_3$) 209.7, 137.1 133.8, 129.0, 128.1, 127.8, 126.7, 59.2, 41.8, 28.3, 24.8, 16.2, 12.2; *m/z* (EI+) 248 (20%, $[M]^+$), 145 (100%, $[M-MeSCH_2CH_2CO]^+$); found $[M+H]^+$ 249.1309, $C_{15}H_{21}OS$ requires 249.1309.

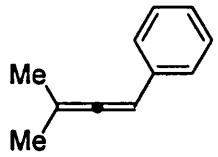
Preparation of 2-methyldeca-2,3-diene 228



The general procedure for the synthesis of allenes (**I**) was followed employing: : 2-methylbut-3-yn-2-yl acetate **209** (1.00 g, 7.9 mmol), Et_2O (50 mL), CuBr (110 mg,

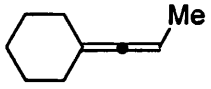
0.79 mmol) and HexMgBr (2 M in diethyl ether) (4.34 mL, 8.7 mmol). Flash chromatography yielded the title compound **228** as a colourless oil (0.66 g, 55%). ν_{max} (film)/cm^{-1} 2962, 1447, 1216; δ_H (300 MHz; $CDCl_3$) 4.95-4.85 (1H, m, C*CH*), 1.93 (2H, app. q. *J* 6.7, CH*CH*$_2$), 1.68 (3H, s, *Me*C), 1.67 (3H, s, *Me*C), 1.33-1.22 (8H, m, 4 × *CH*$_2$), 0.88 (3H, t, *J* 6.7, CH_2*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 201.8, 94.7, 88.9, 34.2, 32.0, 29.8, 28.8, 22.8, 22.4, 20.8, 14.1. Data consistent with the literature.[168]

Preparation of 1-(3-methylbuta-1,2-dienyl)benzene 229



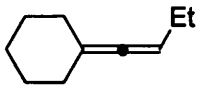
The general procedure for the synthesis of allenes (**I**) was followed employing: : 2-methylbut-3-yn-2-yl acetate **209** (1.00 g, 7.9 mmol), Et_2O (50 mL), CuBr (110 mg, 0.79 mmol) and PhMgBr (3 M in diethyl ether) (2.91 mL, 8.7 mmol). Flash chromatography yielded the title compound **229** as a colourless oil (0.77 g, 68%). ν_{max} (film)/cm^{-1} 2978, 2361, 1468, 1226; δ_H (300 MHz; $CDCl_3$) 7.60-7.13 (5H, m, *Ar-H*), 5.98 (1H, m, CC*CH*), 1.81 (3H, s, C*CH*$_3$), 1.80 (3H, s, C*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 203.6, 128.7, 128.5, 127.3, 126.6, 99.1, 92.6, 20.3 (2 CH_3). Data consistent with the literature.[172]

Preparation of prop-1-enylidenecyclohexane 230



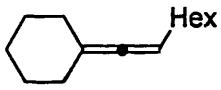
The general procedure for the synthesis of allenes (**I**) was followed employing: 1-cyclohexylprop-2-ynyl acetate **210** (1.00 g, 6.0 mmol), Et_2O (30 mL), CuBr (86 mg, 0.6 mmol) and MeMgBr (3 M in diethyl ether) (2.20 mL, 6.6 mmol). Flash chromatography yielded the title compound **230** as a colourless oil (0.29 g, 40%). ν_{max} (film)/cm^{-1} 2921, 2849, 1442, 1242; δ_H (300 MHz; $CDCl_3$) 5.00-4.90 (1H, m, Me*CH*), 2.14-2.09 (2H, m, C(CH*H*)$_2$), 2.11 (3H, d, *J* 11.3, *Me*CH), 1.68-1.49 (6H, m, C(C*H*H)$_2$(*CH*$_2$)$_2$), 1.38-1.25 (2H, m, CCH_2CH_2*CH*$_2$); δ_C (75 MHz; $CDCl_3$) 199.5, 102.0, 83.5, 32.1, 27.9, 26.6, 14.4. Data consistent with the literature.[173]

Preparation of but-1-enylidenecyclohexane 231



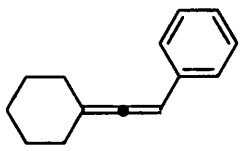
The general procedure for the synthesis of allenes (**I**) was followed employing: 1-cyclohexylprop-2-ynyl acetate **210** (1.00 g, 6.0 mmol), Et_2O (30 mL), CuBr (86 mg, 0.6 mmol) and EtMgBr (3 M in diethyl ether) (2.20 mL, 6.6 mmol). Flash chromatography yielded the title compound **231** as a colourless oil (0.36 g, 44%). ν_{max} (film) /cm^{-1} 2921, 1442, 1237; δ_H (300 MHz; $CDCl_3$) 4.99-4.92 (1H, m, CC*CH*), 2.10-1.96 (4H, m, C(CH_2)$_2$), 1.94-1.85 (2H, m, CH_2CH_3), 1.57-1.41 (6H, m, $CH_2CH_2CH_2CH_2CH_2$), 0.91 (3H, t, *J* 7.0, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 198.2, 103.5, 90.8, 32.3, 28.0, 26.6, 22.7, 14.4. Data consistent with the literature.[174]

Preparation of oct-1-enylidenecyclohexane 232



The general procedure for the synthesis of allenes (**I**) was followed employing: 1-cyclohexylprop-2-ynyl acetate **210** (1.00 g, 6.0 mmol), Et_2O (30 mL), CuBr (86 mg, 0.6 mmol) and HexMgBr (2 M in diethyl ether) (3.31 mL, 6.6 mmol). Flash chromatography yielded the title compound **232** as a colourless oil (0.75 g, 65%). ν_{max} (film) /cm^{-1} 2952, 2356, 1457; δ_H (300 MHz; $CDCl_3$) 4.91-4.84 (1H, m, *CH*), 2.07-2.00 (4H, m, CC(CH_2)$_2$), 1.91-1.84 (2H, m, CCHCH_2), 1.55-1.38 (6H, m, CC(CH_2)$_2$(CH_2)$_2$ and CCHCH$_2$CH_2), 1.30-1.15 (8H, m, CC(CH_2)$_2$(CH_2)$_2$$CH_2$ and CCHCH$_2$CH$_2$$CH_2$$CH_2$$CH_2$) 0.81 (3H, t, *J* 7.0, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 198.7, 110.3, 89.1, 32.3, 32.2, 32.1, 30.1, 29.1, 27.9, 26.6, 23.1, 14.5.

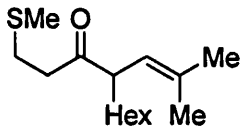
Preparation of 1-(2-cyclohexylidenevinyl)benzene 233



The general procedure for the synthesis of allenes (**I**) was followed employing: 1-cyclohexylprop-2-ynyl acetate **210** (1.00 g, 6.0 mmol), Et_2O (30 mL), CuBr (86 mg, 0.6 mmol) and PhMgBr (3 M in diethyl ether) (2.20 mL, 6.6 mmol). Flash

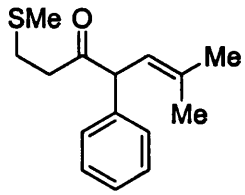
chromatography yielded the title compound **233** as a colourless oil (0.71 g, 64%). ν_{max} (film) /cm^{-1} 2921, 2839, 1452, 1262; δ_H (300 MHz; $CDCl_3$) 7.53-7.06 (5H, m, Ar), 5.91 (1H, br. s, Ph*CH*), 2.22-2.07 (2H, m, C(CH*H*)$_2$), 1.66-1.42 (4H, m, *CH*$_2$CH$_2$CCH$_2$*CH*$_2$), 1.26-1.10 (2H, m, C(C*H*H)$_2$), 0.82-0.78 (CCH$_2$CH$_2$*CH*$_2$); δ_C (75 MHz; $CDCl_3$) 200.1, 136.6, 128.9, 126.9, 126.7, 106.9, 92.8, 31.7, 28.1, 26.5. Data consistent with the literature.[167]

Preparation of 4-(2-methylprop-1-enyl)-1-(methylthio)decan-3-one 234



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 2-methyldeca-2,3-diene **228** (46 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **234** as a yellow oil (28 mg, 74%); ν_{max} (film) /cm^{-1} 2936, 1699, 1452, 913; δ_H (300 MHz; $CDCl_3$) 4.96 (1H, br. d, *J* 9.8, *CH*C(Me)$_2$), 3.26 (1H, ddd, *J* 9.8, 8.0, 6.2, CO*CH*), 2.78-2.62 (4H, m, MeS*CH*$_2$*CH*$_2$), 2.10 (3H, s, *Me*S), 1.74 (3H, d, *J* 1.2, CHC*Me*Me), 1.69 (3H, d, *J* 1.3, CHCMe*Me*), 1.46-1.15 (10H, m, 5 × *CH*$_2$), 0.87 (3H, t, *J* 6.7, CH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 210.2, 135.7, 122.8, 52.7, 40.8, 31.7, 31.5, 29.3, 28.1, 27.1, 25.9, 22.6, 18.4, 15.8, 14.1; *m/z* (EI+) 256 (60%, $[M]^+$), 208 (50%, $[M\text{-}MeSH]^+$), 153 (100%, $[M\text{-}MeSCH_2CH_2CO]^+$); found $[M+H]^+$ 257.1938, $C_{15}H_{29}OS$ requires 257.1934.

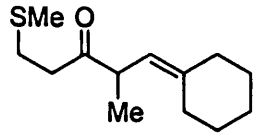
Preparation of 6-methyl-1-(methylthio)-4-phenylhept-5-en-3-one 235



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-

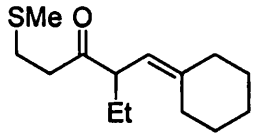
methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(3-methylbuta-1,2-dienyl)benzene **229** (43 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **235** as a yellow oil (26 mg, 69%); ν_{max} (film) /cm^{-1} 3049, 2680, 1709, 1416, 1262; δ_H (300 MHz; $CDCl_3$) 7.32-7.16 (5H, m, Ar), 5.59-5.54 (1H, m, PhCH*CH*), 4.49 (1H, d, *J* 9.4 Ph*CH*CH), 2.75-2.54 (4H, m, MeS*CH_2CH_2*), 1.95 (3H, s, *Me*S), 1.71 (3H, d, *J* 1.2 C*CH_3*), 1.61 (3H, d, *J* 1.3, C*CH_3*); δ_C (75 MHz; $CDCl_3$) 207.8, 139.3, 136.0, 129.3, 128.5, 127.5, 121.7, 58.7, 41.1, 28.6, 26.4, 18.7, 16.1; *m/z* (EI +) 248 (10%, $[M]^+$), 145 (100%, $[M\text{-}MeSCH_2CH_2CO]^+$), 103 (20%, $[M\text{-}Me_2CCHCHPh]^+$); found $[M+H]^+$ 249.1308, $C_{15}H_{21}OS$ requires 249.1308.

Preparation of 1-cyclohexylidene-2-methyl-5-(methylthio)pentan-3-one 236



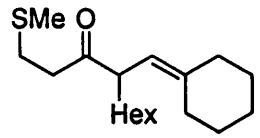
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and prop-1-enylidenecyclohexane **230** (37 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **236** as a yellow oil (26 mg, 78%); ν_{max} (film) /cm^{-1} 3055, 1704, 1416, 1257; δ_H (300 MHz; $CDCl_3$) 4.87 (1H, d, *J* 9.7 COCH*CH*), 3.36 (1H, dq, *J* 9.7, 6.8 CO*CH*CH), 2.76-2.54 (4H, m, MeS*CH_2CH_2*), 2.16-2.14 (2H, m, C*CH_2*$CH_2CH_2CH_2CH_2$), 2.05-1.98 (2H, m, $CCH_2CH_2CH_2CH_2$*CH_2*), 2.03 (3H, s, *Me*S), 1.62-1.44 (6H, m, CCH_2*$CH_2CH_2CH_2$*CH_2), 1.05 (3H, d, *J* 6.8 CH*CH_3*); δ_C (75 MHz; $CDCl_3$) 210.9, 143.3, 120.9, 46.1, 40.5, 37.6, 29.7, 28.8, 28.6, 28.2, 27.1, 16.9, 16.2; *m/z* (EI+) 226 (5% $[M]^+$), 123 (75%, $[M\text{-}MeSCH_2CH_2CO]^+$), 82 (100%, $[M\text{-}Cy]^+$); found $[M+H]^+$ 227.1464, $C_{13}H_{23}OS$ requires 227.1462.

Preparation of 4-(cyclohexylidenemethyl)-1-(methylthio)hexan-3-one 237



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and but-1-enylidenecyclohexane **231** (57 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **237** as a yellow oil (29 mg, 81%); ν_{max} (film) /cm^{-1} 2972, 1653, 1473, 1365, 1160; δ_H (300 MHz; $CDCl_3$) 4.81 (1H, d, *J* 9.9, COCH*CH*), 3.71 (1H, ddd, *J* 9.8, 8.2, 6.0, CO*CH*CH), 2.73-2.55 (4H, m, MeS*CH₂CH₂*), 2.19-2.12 (2H, m, CHC*CH₂*), 2.08-2.04 (2H, m, CHC*CH₂*), 2.03 (3H, s, *Me*S), 1.74-1.60 (1H, m, $CHCH_aH_bCH_3$), 1.53-1.46 (6H, m, $CCH_2CH_2CH_2CH_2CH_2$), 1.43-1.28 (1H, m, $CHCH_aH_bCH_3$), 0.78 (3H, t, *J* 7.4); δ_C (75 MHz; $CDCl_3$) 210.7, 144.5, 119.5, 53.7, 41.1, 37.7, 29.8, 29.0, 28.5, 28.2, 27.1, 24.8, 16.2, 12.1; *m/z* (EI+) 240 (5%, $[M]^+$), 137 (55%, $[M\text{-}MeSCH_2CH_2CO]^+$), 95 (100%, $[M\text{-}MeSCH_2CH_2COCHCH_2CH_3]^+$); found $[M+H]^+$ 241.1621, $C_{14}H_{25}OS$ requires 241.1621.

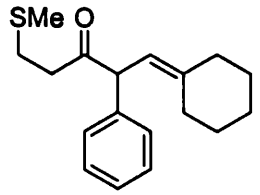
Preparation of 4-(cyclohexylidenemethyl)-1-(methylthio)decan-3-one 238



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and oct-1-enylidenecyclohexane **232** (58 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **238** as a yellow oil (40 mg, 89%); ν_{max} (film) /cm^{-1} 2936, 1709, 1468, 903; δ_H (300 MHz; $CDCl_3$) 4.82 (1H, d, *J* 9.8, COCH*CH*), 3.24 (1H, ddd, *J* 9.8, 8.2, 5.9, CO*CH*CH), 2.74-2.55 (4H, m, MeS*CH₂CH₂*), 2.18-2.12 (2H, m, $CCH_2CH_2CH_2CH_2CH_2$), 2.07-2.05 (2H, m, $CCH_2CH_2CH_2CH_2CH_2$), 2.03 (3H, s, *Me*S), 1.68-1.58 (1H, m, $CHCH_aH_bCH_2CH_2$), 1.52-1.48 (6H, m, $CCH_2CH_2CH_2CH_2CH_2$), 1.39-1.28 (1H, m, $CHCH_aH_bCH_2CH_2$),

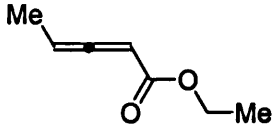
1.24-1.08 (8H, m, $CHCH_2CH_2CH_2CH_2CH_2CH_3$), 0.80 (3H, t, *J* 6.7, $CHCH_2CH_2CH_2CH_2CH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 210.7, 144.2, 119.8, 52.0, 41.1, 37.7, 32.1, 31.7, 29.8, 29.6, 29.0, 28.9, 28.5, 27.5, 27.1, 23.0, 16.2, 14.5; *m/z* (EI) 296 (5%, $[M]^+$), 193 (40%, $[M\text{-}MeSCH_2CH_2CO]^+$), 109 (100%, $[M\text{-}CH_3(CH_2)_5C_2]^+$); found $[M+H]^+$ 296.2169, $C_{18}H_{33}OS$ requires 296.2168.

Preparation of 1-cyclohexylidene-5-(methylthio)-2-phenylpentan-3-one 239



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(2-cyclohexylidenevinyl)benzene **233** (55 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **239** as a yellow oil (27 mg, 62%); ν_{max} (film) /cm^{-1} 3044, 1714, 1427, 1263; δ_H (300 MHz; $CDCl_3$) 7.31-7.15 (5H, m, Ph), 5.49 (1H, dt, *J* 9.1, 1.0, PhCH*CH*), 4.58 (1H, d, *J* 9.4, Ph*CH*CH), 2.71-2.54 (4H, m, $MeSCH_2CH_2$), 2.14-1.94 (7H, m, *Me*S and $C(CH_2)_2$), 1.51-1.36 (6H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 207.9, 144.0, 139.6, 129.2, 128.5, 127.4, 118.3, 57.7, 37.7, 29.8, 28.8, 27.9, 27.0, 23.1; *m/z* (EI+) 288 (10% $[M]^+$), 185 (90%, $[M\text{-}MeSCH_2CH_2CO]^+$), 117 (100%, $[M\text{-}CyCCPh]^+$); found $[M+H]^+$ 289.1622, $C_{18}H_{25}OS$ requires 289.1621.

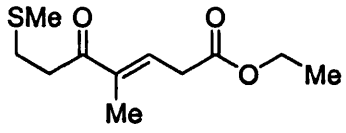
The general procedure for the synthesis of allenic esters (J) as exemplified by ethyl penta-2,3-dienoate 244



To (carbethoxymethylene)triphenylphosphorane (10.00 g, 29 mmol) in DCM (80 mL) at 10 °C NEt_3 (4.00 mL, 29 mmol) in DCM (30 mL) was added dropwise over 5 minutes. After this time the resulting solution was stirred for 10 minutes and then

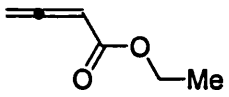
propionyl chloride (2.50 mL, 29 mmol) was added dropwise over 15 minutes with vigorous stirring. The resulting mixture was stirred for 30 minutes at room temperature before it was reduced *in vacuo*. Pentane (100 mL) was added to the resulting slurry and allowed to stand for 2 hours with periodic shaking. The precipitate was removed *via* filtration and the filter cake washed with pentane (50 mL). The filtrate was reduced *in vacuo* to 0.25% of the original amount and once more filtered. The filtrate was reduced *in vacuo* and purified by flash chromatography (1:9, Et_2O: Pentane) to yield the title compound **244** as a colourless oil (2.33 g, 64%); ν_{max} (film) /cm^{-1} 2972, 1956, 1714, 1144; δ_H (300 MHz; $CDCl_3$) 5.56-5.46 (2H, m, Me*CHCCH*), 4.12 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 1.71 (3H, dd, *J* 7.1, 3.6, *Me*CH), 1.21 (3H, t, *J* 7.1, OCH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 211.9, 165.2, 89.2, 86.7, 59.8, 21.3, 13.2. Data consistent with the literature.[175]

Preparation of (*E*)-ethyl 4-methyl-7-(methylthio)-5-oxohept-3-enoate 243



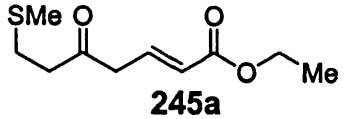
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(dppe)]ClO_4 (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and ethyl penta-2,3-dienoate **242** (38 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (2:8, Et_2O:Hexane) yielded the title compound **243** as a yellow oil. (31 mg, 96%); ν_{max} (film) /cm^{-1} 2978, 1735, 1663, 1365, 913; δ_H (300 MHz; $CDCl_3$) 6.78-6.72 (1H, m, C*CH*CH$_2$), 4.13 (2H, q, *J* 7.2, O*CH*$_2$CH$_3$), 3.22 (2H, d, *J* 6.8, CH*CH*$_2$CO), 2.95 (2H, t, *J* 7.3, CH$_2$*CH*$_2$CO), 2.71 (2H, t, *J* 7.3, *CH*$_2$CH$_2$CO), 2.06 (3H, s, *Me*S), 1.73 (3H, d, *J* 1.1, *Me*CCH), 1.22 (3H, t, *J* 7.2, OCH$_2$*CH*$_3$); δ_C (75 MHz; $CDCl_3$) 199.9, 175.5, 139.7, 133.8, 61.6, 37.7, 34.8, 29.3, 16.2, 14.8, 12.1; *m/z* (ES+) 230 (100% $[M]^+$), 182 (80%, $[M\text{-}MeSH]^+$); found $[M+H]^+$ 231.1048, $C_{11}H_{19}O_3S$ requires 231.1049.

Preparation of ethyl buta-2,3-dienoate 244

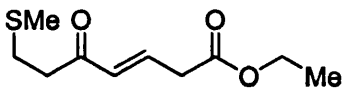


The general procedure for the hydroacylation reaction (**C**) (carbethoxymethylene)triphenylphosphorane (10.00 g, 29 mmol) in DCM (80 mL), NEt_3 (4.00 mL, 29 mmol) in DCM (30 mL) and acetyl chloride (2.10 mL, 29 mmol) in DCM (30 mL). Flash chromatography (1:9, Et_2O: Pentane) yielded the title compound **244** as a colourless oil (1.94 g, 60%); ν_{max} (film) /cm^{-1} 2983, 1971, 1709, 1262, 1041, 857; δ_H (300 MHz; $CDCl_3$) 5.56 (1H, t, *J* 6.6, CH_2CHCO), 5.14 (2H, d, *J* 6.6, CH_2CHCO), 4.13 (2H, q, *J* 7.1, OCH_2CH_3), 1.22 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 214.7, 164.7, 87.1, 78.2, 60.0, 13.0. Data consistent with the literature.[176]

Preparation of (*E*)-ethyl 7-(methylthio)-5-oxohept-2-enoate 245a and (*E*)-ethyl 7-(methylthio)-5-oxohept-3-enoate 245b



245a

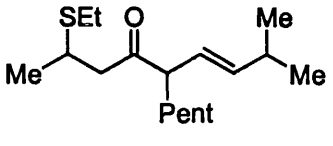


245b

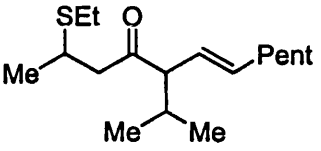
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and ethyl buta-2,3-dienoate **244** (34 mg, 0.3 mmol). Heated at 55 °C for 8 hours. Flash chromatography (2:8, Et_2O:Hexane) yielded the title compounds **245a** and **245b** as an inseparable mixture (1:1 **245a**: **245b**) as a yellow oil. (26 mg, 81%); ν_{max} (film) /cm^{-1} 2983, 1791, 1719, 1440, 1375, 1160; δ_H (300 MHz; $CDCl_3$) ((*E*)-ethyl 7-(methylthio)-5-oxohept-2-enoate **245a**) 6.96 (1H, dt, *J* 15.7, 7.2, $CHCHCO_2Et$), 5.84 (1H, dt, *J* 15.7, 1.5, $CHCO_2Et$), 4.17-4.08 (2H, m, OCH_2CH_3) 3.31-3.28 (2H, m, $COCH_2CH$), 2.74-2.65 (4H, m, $MeSCH_2CH_2$), 2.05 (3H, s, *Me*S), 1.22 (3H, t, *J* 6.0, OCH_2CH_3); δ_H (300 MHz; $CDCl_3$) ((*E*)-ethyl 7-(methylthio)-5-oxohept-3-enoate **245b**) 6.85 (1H, dt, *J* 16.1, 7.1, $CHCHCO_2Et$), 6.13 (1H, dt, *J* 16.1, 1.5, $CHCO_2Et$), 4.17-4.08 (2H, m, OCH_2CH_3) 3.19 (2H, dd, *J* 7.1 1.5, $COCH_2CH$), 2.83 (2H, t, *J* 8.5, CH_2COCH), 2.74-2.65 (2H, m, $MeSCH_2$), 2.06 (3H, s, *Me*S), 1.23 (3H, t, *J* 5.9, OCH_2CH_3); δ_C (75

MHz; $CDCl_3$) (both) 205.2, 198.4, 170.2, 166.1, 139.8, 138.8, 135.0, 125.6, 61.7, 60.9, 46.2, 42.9, 40.2, 38.1, 30.1, 28.5, 28.1, 16.2, 14.6, 14.5.

Preparation of (*E*)-2-(ethylthio)-5-(3-methylbut-1-enyl)undecan-4-one and (*E*)-2-(ethylthio)-5-isopropyltridec-6-en-4-one



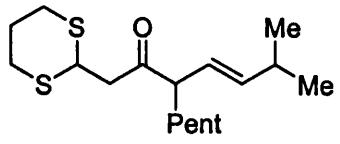
246a



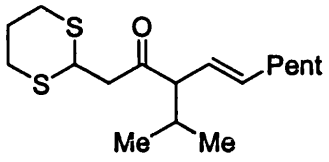
246b

The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-3-(ethylthio)butanal (20 μL, 0.15 mmol) and 2-methyldeca-3,4-diene **219** (46 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (2:8, Et_2O:Hexane) yielded the title compounds **246a and 246b** as a yellow oil. (ration **a:b** 8:1, 32 mg, 74%); ν_{max} (film) /cm^{-1} 3049, 1709, 1416, 1262, 893; δ_H (300 MHz; $CDCl_3$) (**243a**) 5.49 (1H, dd, *J* 6.6, 15.5, COCH*CH*CH), 5.19-5.06 (1H, m, CH*CH*CH$(CH_3)_2$), 3.30-3.16 (1H, m, CO*CH*), 2.94-2.84 (1H, m, *CH*$(CH_3)_2$), 2.75-2.42 (4H, m, $CH_3CH_2SCHCH_2$), 2.27-2.12 (1H, m, CH_3CHSEt), 1.21-1.14 (11H, m, $CH_2CH_2CH_2CH_2CH_3$ and CH_3CHSEt), 0.90 (6H, d, *J* 6.7, CH$(CH_3)_2$), 0.85-0.76 (6H, m, CH_3CH_2S and CH_2CH_3); δ_H (300 MHz; $CDCl_3$) (**243b**) 5.48 (1H, dd, *J* 6.5, 15.2, COCH*CH*CH), 5.19-5.06 (1H, m, CH*CH*CHCH_2), 3.30-3.16 (1H, m, CO*CH*), 2.94-2.84 (1H, m, *CH*$(CH_3)_2$), 2.75-2.42 (4H, m, $CH_3CH_2SCHCH_2$), 2.27-2.12 (1H, m, CH_3CHSEt), 1.21-1.14 (11H, m, $CH_2CH_2CH_2CH_2CH_3$ and CH_3CHSEt), 0.98 (6H, d, *J* 6.6, CH$(CH_3)_2$), 0.85-0.76 (6H, m, CH_3CH_2S and CH_2CH_3);δ_C (75 MHz; $CDCl_3$) (both) 208.9, 208.7, 148.6, 140.7, 123.7, 123.5, 75.6, 56.0, 47.6, 47.6, 43.8, 34.6, 33.4, 33.3, 30.7, 30.6, 30.1, 29.9, 28.8, 28.5, 27.2, 25.7, 24.8, 23.8, 23.7, 21.6, 21.4, 21.3, 20.5, 19.8, 13.8, 13.0; *m/z* (EI+) 284 (5% $[M]^+$), 181 (90%, $[M\text{-}EtSCH(CH_3)CH_2]^+$), 89 (100%, $[M\text{-}CH_2COCH(Pent)CHCHCH(CH_3)_2]^+$); found $[M+H]^+$ 285.2250, $C_{17}H_{33}OS$ requires 285.2247.

Preparation of (*E*)-1-(1,3-dithian-2-yl)-3-(3-methylbut-1-enyl)octan-2-one and (*E*)-1-(1,3-dithian-2-yl)-3-isopropylundec-4-en-2-one



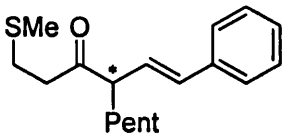
247a



247b

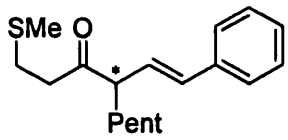
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 2-(1,3-dithian-2-yl)acetaldehyde (25 mg, 0.15 mmol) and 2-methyldeca-3,4-diene **219** (46 mg, 0.3 mmol). Heated at 55 °C for 16 hours. Flash chromatography (2:8, Et_2O:Hexane) yielded the title compounds **247a and 247b** as a yellow oil. (ratio **a:b** 10:1, 39 mg, 82%); ν_{max} (film)/cm^{-1} 3060, 1714, 1416, 1267; δ_H (300 MHz; $CDCl_3$) (**247a**) 5.50 (1H, ddd, *J* 15.4, 6.7, 0.5, *CH*CHCH$(CH_3)_2$), 5.12 (1H, ddd, *J* 15.4, 9.0, 1.2, *CH*CH$(CH_3)_2$), 4.45 (1H, t, *J* 6.8, *CH*CH_2), 2.97-2.82 (4H, m, *CH*$_2$CO*CH*CHCH*CH*), 2.79-2.70 (4H, m, S*CH*$_2$$CH_2$*CH*$_2$S), 2.27-2.16 and 2.09-1.99 (2H, m, SCH$_2$*CH*$_2$$CH_2$S), 1.84-1.57 (2H, m, CH*CH*$_2$$CH_2$), 1.41-1.11 (6H, m, CH_2*CH*$_2$*CH*$_2$*CH*$_2$$CH_3$), 0.91 (6H, d, *J* 6.8, CH(*CH*$_3$)$_2$), 0.80 (3H, t, *J* 6.5, *CH*$_3$$CH_2$); δ_C (75 MHz; $CDCl_3$) 207.3, 142.7, 124.6, 57.5, 46.5, 41.6, 32.0, 31.6, 31.0, 30.8, 27.1, 25.7, 22.9, 22.7, 14.4; δ_H (300 MHz; $CDCl_3$) (**247b**) 5.49-5.45 (1H, m, *CH*CHCH$(CH_3)_2$), 5.21-2.13 (1H, m, *CH*CH$(CH_3)_2$), 4.49 (1H, t, *J* 6.9, *CH*CH_2), 2.97-2.82 (4H, m, *CH*$_2$CO*CH*CHCH*CH*), 2.79-2.70 (4H, m, S*CH*$_2$$CH_2$*CH*$_2$S), 2.27-2.16 and 2.09-1.99 (2H, m, SCH$_2$*CH*$_2$$CH_2$S), 1.84-1.57 (2H, m, CH*CH*$_2$$CH_2$), 1.41-1.11 (6H, m, CH_2*CH*$_2$*CH*$_2$*CH*$_2$$CH_3$), 0.98 (6H, d, *J* 6.5, CH(*CH*$_3$)$_2$), 0.79 (3H, t, *J* 7.6, *CH*$_3$$CH_2$);*m/z* (EI+) (both) 314 (10% $[M]^+$), 271 (20%, $[M\text{-}CH(CH_2)_3]^+$), 119 (100%, $[M\text{-}CH_2COCH(Pent)CHCHCH(CH_3)_2]^+$); found $[M+H]^+$ 315.1813, $C_{17}H_{31}OS_2$ requires 315.1811.

The general procedure for the screening of chiral ligands (K) as exemplified by (*E*)-1-(methylthio)-4-styrylnonan-3-one 223



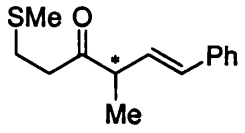
To [Rh(COD)]BF_4 (6 mg, 0.015 mmol) in acetone (1.5 mL), (*R,R*)-Me-Duphos (4.5 mg, 0.015 mmol) was added. Te resulting solution was stirred for 5 minutes after which time the catalyst was activated by bubbling H_2 (g) for 2 minutes. The solution was purged with Ar and 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(octa-1,2-dienyl)benzene **216** (84 mg, 0.45 mmol) were added. The resulting mixture was heated at 55 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **223** as a yellow oil (31 mg, 72%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min. The compound was determined to have *ee* = 72%.

Enantioslective preparation of (*E*)-1-(methylthio)-4-styrylnonan-3-one 223



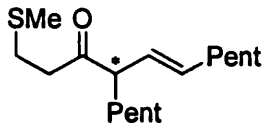
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3 mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(octa-1,2-dienyl)benzene **216** (84 mg, 0.45 mmol). Heated at 40 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **223** as a yellow oil (35 mg, 80%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel OJ-H column (98:2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 17.6 min; enantiomer 2 t_r = 19.6 min. The compound was determined to have *ee* = 83%.

Preparation of *(E)*-4-methyl-1-(methylthio)-6-phenylhex-5-en-3-one 226



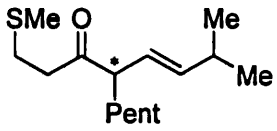
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3 mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 1-(buta-1,2-dienyl)benzene **224** (59 mg, 0.45 mmol). Heated at 40 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **226** as a yellow oil. (30 mg, 88%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel AS-H column (99.5:0.5 hexane:*iso*propanol), 0.3 mL/min; enantiomer 1 t_r = 32.4 min; enantiomer 2 t_r = 61.4 min. The compound was determined to have *ee* = 68%.

Preparation of *(E)*-1-(methylthio)-4-pentylundec-5-en-3-one 221



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3 mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and trideac-6,7-diene **218** (81 mg, 0.45 mmol). Heated at 40 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **221** as a yellow oil (27 mg, 65%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel OJ-H column (99.8:0.2 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 4.8 min; enantiomer 2 t_r = 5.2 min. The compound was determined to have *ee* = 82%.

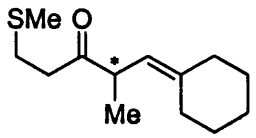
Preparation of (E)-4-(3-methylbut-1-enyl)-1-methylthio)nonan-3-one 222



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3

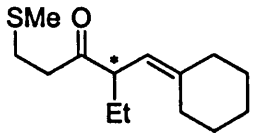
mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and 2-methyldeca-3,4-diene **219** (69 mg, 0.45 mmol). Heated at 40 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **222** as a yellow oil (27 mg, 71%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel AS-H column (99.5:0.5 hexane:*iso*propanol), 1.0 mL/min; enantiomer 1 t_r = 11.4 min; enantiomer 2 t_r = 12.8 min. The compound was determined to have *ee* = 49%.

Preparation of 1-cyclohexylidene-2-methyl-5-(methylthio)pentan-3-one 236



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3 mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and prop-1-enylidenecyclohexane **230** (56 mg, 0.45 mmol). Heated at 40 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **236** as a yellow oil (21 mg, 64%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel AS-H column (99:1 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 10.3 min; enantiomer 2 t_r = 11.8 min. The compound was determined to have *ee* = 67%.

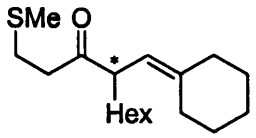
Preparation of 4-(cyclohexylidenemethyl)-1-(methylthio)hexan-3-one 237



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3 mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and but-1-enylidenecyclohexane **231** (89 mg, 0.45 mmol). Heated at 40 °C for 24 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **237** as a yellow oil (26 mg, 75%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel AS-H column (99.7:0.3 hexane:*iso*propanol), 1.0 mL/min;

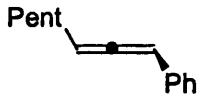
enantiomer 1 t_r = 14.8 min; enantiomer 2 t_r = 16.2 min. The compound was determined to have *ee* = 48%.

Preparation of 4-(cyclohexylidenemethyl)-1-(methylthio)decan-3-one 238



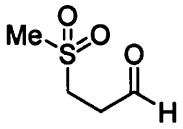
The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst [Rh(NBD)(*R,R*)-Me-Duphos]ClO_4 (9 mg, 0.015 mmol), acetone (0.3 mL), $CHCl_3$ (1.2 mL), 3-methylthiol propionaldehyde (15 μL, 0.15 mmol) and oct-1-enylidenecyclohexane **232** (87 mg, 0.45 mmol). Heated at 40 °C for 48 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the title compound **238** as a yellow oil (34 mg, 76%). Data consistent to that reported earlier. Product ratios were determined by HPLC with a Chiracel AS-H column (99.5:0.5 hexane:*iso*propanol), 0.5 mL/min; enantiomer 1 t_r = 8.8 min; enantiomer 2 t_r = 9.8 min. The compound was determined to have *ee* = 36%.

Preparation of (S)-1-(octa-1,2-dienyl)benzene 216



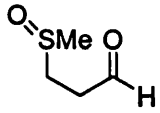
The general procedure for the synthesis of allenes (**I**) was followed employing: (*R*)-Oct-1-yn-2-yl acetate (1 g, 5.9 mmol), Et_2O (30 mL), CuBr (0.09 g, 0.6 mmol), PhMgBr (3M in diethyl ether) (2.2 mL, 6.5 mmol). Flash chromatography yielded 1-(*S*) (P)-(octa-1,2-dienyl)benzene **216** as a colourless oil (0.74 g, 68%). %). Data consistent to that reported earlier. $[\alpha]_D^{21}$ +290 (c = 0.97, MeCN). Product ratios were determined by HPLC with a Chiracel OD-H column (hexane), 0.3 mL/min; enantiomer 1 t_r = 19.5 min; enantiomer 2 t_r = 22.8 min. The compound was determined to have *ee* = 99%.[145]

Preparation of 3-(methylsulfonyl)propanal 260



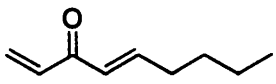
To 3-methylthio propionaldehyde (0.31 mL, 3.0 mmol) in DCM (25 mL) at 0 °C *m*CPBA 77% (1.56 g, 7.0 mmol) in DCM (25 mL) was added dropwise. The resulting solution was then stirred at room temperature overnight. It was then reduced *in vacuo* and purified by flash column chromatography (3:7, EtOAc: Hexane) to yield the title compound **260** as a white solid (0.28 g, 70%); ν_{max} (film) /cm^{-1} 3162, 2238, 1791, 1714, 1468, 1375; δ_H (300 MHz; $CDCl_3$) 9.77 (1H, s, C*H*O), 3.30 (2H, t, *J* 7.1, $MeSO_2CH_2$), 3.05 (2H, t, *J* 7.1, CH_2CH_2CHO), 2.90 (3H, s, $MeSO_2$); δ_C (75 MHz; $CDCl_3$) 197.5, 47.8, 42.0, 36.5; Anal. Calc. for $C_4H_8O_3S$: C, 35.28, H, 5.92. Found C, 34.8, H, 5.83%.

Preparation of 3-(methylsulfinyl)propanal 261



To 3-methylthio propionaldehyde (0.31 mL, 3.0 mmol) in DCM (25 mL) at 0 °C *m*CPBA 77% (690 mg, 3.1 mmol) in DCM (25 mL) was added dropwise. The resulting solution was then stirred at room temperature overnight. It was then reduced *in vacuo* and purified by flash column chromatography (3:7, EtOAc: Hexane) to yield the title compound **261** as a colourless oil (198 mg, 55%); ν_{max} (film) /cm^{-1} 2960, 2610, 1740, 1660, 1200, 1137, 930; δ_H (300 MHz; $CDCl_3$) 9.84 (1H, s, C*H*O), 3.11-2.81 (4H, m, CH_2CH_2CHO), 2.58 (3H, s, *Me*SO); δ_C (75 MHz; $CDCl_3$) 198.5, 45.8, 38.9, 36.1; Data consistent to the literature.[177]

Preparation of (*E*)-nona-1,4-dien-3-one 262



The general procedure for the hydroacylation reaction (**C**) was followed employing pre-catalyst $[Rh(NBD)(dppe)]ClO_4$ (10 mg, 0.015 mmol), acetone (1.5 mL), 3-(methylsulfinyl)propanal (18 mg, 0.15 mmol) and 1-hexyne (106 μL, 3 mmol).. Heated at 55 °C for 16 hours. Flash chromatography (1:9, Et_2O:Hexane) yielded the

title compound **262** as a yellow oil (15 mg, 72%); ν_{max} (film) /cm^{-1} 2967, 2248, 1786, 1478, 903; δ_H (300 MHz; $CDCl_3$) 6.95 (1H, dt, *J* 15.7, 7.0, COCH*CH*), 6.61 (1H, dd, *J* 17.4, 10.5, CH_2*CH*CO), 6.36 (1H, dt, *J* 15.7, 1.3, CO*CH*CH), 6.28 (1H, dd, *J* 17.3, 1.3 *CH*HCHCO), 5.81 (1H, dd, *J* 15.7, 1.3, *CH*HCHCO), 2.30-2.22 (2H, m, CHCH*CH_2*), 1.34-1.62 (4H, m, *CH_2CH_2*CH_3), 0.92 (3H, t, *J* 7.1, CH_2*CH_3*); δ_C (75 MHz; $CDCl_3$) 189.3, 148.7, 134.6, 127.9, 32.3, 30.2, 22.2, 13.8. Data consistent with the literature.[178]

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